PART 1: COMBINATORIAL SYNTHESIS OF *N*-HETEROCYCLES

PART 2: DEVELOPMENT OF A POLYMER-SUPPORTED HANTZSCH ESTER

HE RONGJUN

(B.Sc., HUBEI UNIVERSITY)

A THESIS SUBMITTED

FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

NATIONAL UNIVERSITY OF SINGAPORE

2007

Acknowledgements

I would like to express my heartfelt gratitude to my supervisor, Dr. Lam Yulin, for her invaluable guidance, continuous flow of ideas, source of inspiration and warm-hearted care during my studies. Although extremely busy with her schedule, she is always available for helpful discussion and encouragement.

I am thankful to Dr. Patrick H Toy, Department of Chemistry at University of Hong Kong, for his stimulating suggestions on part 2 of my thesis.

I am also grateful to Assoc. Prof. Go Mei Lin for allowing me to use her microwave reactor.

Special thanks go to the following people for their gracious help and warm friendship:

- all my lab partners: Che Jun, Ching Shi Min, Fang Zhanxiong, Fu Han, Gao Yongnian, Kong Kah Hoe, and Makam Shantha Kumar Raghavendra. Without them, the research life could not be so enjoyable and fulfilling.

- Many teachers and my friends in Department of Chemistry at NUS who provided help and support during this time.

- Staff from the NMR, MS, Chromatography laboratories and lab supplies who with cheerfulness and patience helped me greatly in the analyses and purchasing of chemicals.

Acknowledgement is also recorded for the Research Scholarship provided by the National University of Singapore for the period of August 2003 to April 2007.

Lastly, I could not have done this project without the sustaining love and encouragement from my girlfriend Nguyen Thi Thuy Linh and my family members.

Table of Contents

Part 2: Development of a Polymer-Supported Hantzsch Ester

Chapter 5 Development of a Polymer-Supported Hantzsch Ester

Summary

This thesis is composed by two parts: Combinatorial Synthesis of *N*-Heterocycles (Part 1) and Development of a Polymer-Supported Hantzsch Ester (Part 2).

Part 1 comprises four projects focusing on the development of solid-phase synthetic methodologies for preparing pharmaceutically and medicinally important *N*-heterocycles.

The first two projects aim to develop solid-phase synthetic routes toward xanthines. Efforts in the first project has resulted in a highly efficient and scaleable synthetic procedure affording 1,3-substituted xanthines. This was the first reported traceless solid-phase synthesis of 1,3-substituted xanthines. The solid-phase synthesis was achieved using PS-MB-CHO resin. Cyclocondensation of the polymer-bound aminoimidazole with isocyanates followed by alkylation provided 1,3-substituted xanthines. A representative set of 12 xanthines and 4 thioxanthines was prepared.

In the second project, a traceless solid-phase route to substituted xanthines based on the late stage pyrimidine ring closure was developed. This method was found to be especially useful for the preparation of xanthines containing a variety of substituents at the N1, N3, N7 and C8 positions. These subsituents could be introduced onto the xanthine ring in an unambiguous manner. A library of 22 compounds was prepared.

The third project investigated the combinatorial solution-phase parallel synthesis of polycyclic guanines. A highly efficient synthetic route involving 9 steps was developed. Unlike previous syntheses of polycyclic guanines which use 2-chloropurine as the necessary intermediate, this method made use of thioxanthine as the key intermediate. This provided a

more efficient construction of the third ring. To demonstrate the versatility of this chemistry, a set of 6 compounds was prepared.

The fourth project involves the development of a microwave-assisted traceless solid-phase synthetic route to pyrazolidine-3,5-diones. This was the first reported solid-phase synthesis methodology for the preparation of pyrazolidine-3,5-diones. Using our synthetic protocol, we have demonstrated that pyrazolidine-3,5-diones could be obtained in extremely high overall yields. A representative library of 27 pyrazolidine-3,5-diones was prepared.

Part 2 of this thesis focuses on the design, development and applications of a soluble polymer-supported Hantzsch ester as a reducing agent. An efficient synthetic method was developed for the synthesis of this polymer-supported Hantzsch ester. The polymer-supported Hantzsch ester was successfully applied for the reduction of α,β-unsaturated aldehydes, reductive amination between aldehydes and aniline and reduction of benzoquinones.

List of Tables

List of Figures and Schemes

List of Abbreviations

δ	Chemical shift
AIBN	2,2′-Azobis(2-methylpropionitrile)
AIDS	Acquired immune deficiency syndrome
ArgoGel-MB-CHO	4-Formyl-3-methoxyphenoxymethyl poly(ethylene glycol and styrene) resin
ArgoPore-MB-CHO	Highly cross-linked and macroporous, 4-formyl-3-methoxy phenoxymethyl polystyrene resin
AZT	Azidothymidine
BHA resin	Benzylhydrylamine resin
Bn	Benzyl
Boc	Tertiary-butoxycarbonyl
BOP	Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
byp	Byproduct
Bu	Butyl
^{t}Bu	Tertiary-butyl
calcd	Calculated
CC	Column chromatography
CFTR	Cystic fibrosis transmembrane conductance regulator
CH_2Cl_2	Dichloromethane
CLEAR	Cross-linked ethoxylate acrylate resin
m-CPBA	3-Chloroperoxybenzoic acid
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*-Dicyclohexylcarbodiimide
DIEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide

DMSO	Dimethylsulphoxide
EDC	*N*-Ethyl-*N'*-(3-diethylaminopropyl) carbodiimide
EI	Electron impact
ESI	Electrospray ionization
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
Fmoc	Fluorenylmethoxycarbonyl
FTIR/IR	Fourier transform infrared spectroscopy
GC	Gas chromatography
GC-MS	Gas chromatography integrated with mass detector
h	Hour
HAL resin	Hypersensitive acid-labile resin
HIV	Human immunodeficiency virus
HM74A	G-protein-coupled receptor in humans
HMBA resin	4-(Hydroxymethyl)benzoic acid-4-methylbenzhydrylamine resin
HMP	Hydroxymethylphenoxy
HOAc	Acetic acid
HATU	2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HR-MAS	High resolution magic angle spinning
Hycron resin	Pd (0)-sensitive resin with an allylic anchor and a polar spacer
j	Coupling constant
Kaiser oxime resin	4-Nitrobenzophenone oxime resin
Kenner's resin	(4-Sulfamylbenzoyl)-4-methylbenzhydryl-amine resin
m	Multiplet
MAS	Magic angle spinning
MBHA	4-Methylbenzhydrylamine resin
Me	Methyl

MeOH	Methanol
Merrifield's resin	4-Chloromethylphenyl resin
min	Minute
mw	Microwave irradiation
NADH	Reduced nicotinamide adenine dinucleotide
NMR	Nuclear magnetic resonance
p	Product
PDE	Phosphodiesterase
PEG	Polyethylene glycol
PEGA	Polyethylene glycol and polyacrylamide copolymer
Pepsyn	*N*,*N*-dimethylacrylic amide, bis(acrylamidoethane), and *N*-acryloylsarcosine methyl ester copolymer
Pepsyn K	Kieselguhr-supported Pepsyn
Ph	Phenyl
POEPOP	Polyethylene glycol and polyoxypropylene copolymer
POEPS	Polyethylene glycol polymerized onto divinylbenzene cross-linked polystyrene
PolyHIPE	Polyamide with high internal phase emulsion
Pr	Propyl
PS-MB-CHO	4-Formyl-3-methoxyphenoxymethyl polystyrene resin
q	Quartet
REM resin	Regenerable resin linker initially functionalized via a Michael addition
Rink-Acid	4-(2,4-Dimethoxyphenyl-hydroxymethyl)-phenoxy resin
Rink-Amide	4-(2,4-Dimethoxyphenyl-aminomethyl)-phenoxy resin
ROMP	Ring opening metathesis polymerization
RX	Alkyl halides
s	Singlet
SASRIN resin	Super acid sensitive resin

SCAL resin	Safety-catch acid-labile resin
SPS	Solid-phase synthesis
t	Triplet
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TEA	Triethyl amine
Tentagel	Polystyrene and poly(ethlene glycol) copolymer
TFA	Trifluoro acetic acid
TFMSA	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMG	Tetramethylguanidine
TMS	Tetramethylsilane
Trityl resin	1-Chloro-1-(2-chlorophenyl)-1-phenyl-methylpolystyrene resin
UV	Ultraviolet spectroscopy
Wang resin	4-Hydroxymethylphenoxy resin

List of Publications

1) He, R.; Lam, Y. "Combinatorial Solution-Phase Parallel Synthesis of Polycyclic Guanines" *Manuscript in preparation.*

2) He, R.; Toy, P. H.; Lam, Y. "Development of a Polymer-Supported Hantzsch Ester" *Manuscript in preparation.*

3) He, R.; Lam, Y. "A Highly Efficient Combinatorial Synthesis of Pyrazolidine-3,5-Diones Through a Novel Solid-Phase Methodology by Using Ester Exchange Strategy" *Manuscript in preparation.*

4) He, R.; Ching, S.-M.; Lam, Y. "Traceless Solid-Phase Synthesis of Substituted Xanthines" *J. Comb. Chem.* **2006**, *8*, 923-928.

5) He, R.; Lam, Y. "A Highly Efficient Solid-Phase Synthesis of 1,3-Substituted Xanthines" *J. Comb. Chem.* **2005**, *7*, 916-920.

Conference Papers

1) He, R.; Lam, Y. "A Highly Efficient Combinatorial Synthesis of Pyrazolidine-3,5-Diones Through a Novel Solid-Phase Methodology by Using Ester Exchange Strategy" *6th International Symposium by Chinese Inorganic Chemists (ISCIC-6) and 9th International Symposium by Chinese Organic Chemists (ISCOC-9).* Singapore, **2006**, poster presentation.

2) He, R.; Lam, Y. "High Yield Solid-Phase Synthesis of Substituted Xanthines and Thioxanthines" *Pacifichem 2005*. Honolulu, Hawaii, USA, **2005**, poster presentation.

Chapter 1 Introduction

Combinatorial chemistry has its origins in solid-phase peptide synthesis for which Bruce Merrifield was awarded the Nobel Prize in 1984.[1] In solid-phase peptide synthesis, peptide couplings were carried out on a polymeric support which simplified the purification process. This method was so reliable and consistent that in the 1980s, it was used to make many peptides simultaneously in the same reaction container. Houghten's "tea-bag" method was particularly appealing as the same peptide coupling step could be applied to many different polymer-supported peptide sequences simultaneously.[2] Three years later, Furka described a mix-split procedure[3] which was shortly adopted by Houghten[4] and Lam[5] for the synthesis of large numbers of peptides in a very few number of chemical steps. During this time, the concept of combinatorial chemistry was formed.

As the essence of combinatorial chemistry is the ability to generate large numbers of chemical compounds efficiently, it has had important impact on both academic and industrial fields. Today, combinatorial chemistry has become a critical and necessary tool for lead identification and optimization in the drug discovery process where thousands of compounds should be tested per week. It is combinatorial chemistry that changed the way we approach synthetic chemistry and that allowed drug discovery process to be much more efficient compared to previous times. It is for this reason that nearly every pharmaceutical company has now established at least one group working in this area. Besides its application in pharmaceutical research, combinatorial chemistry has also been applied to the optimization of catalyst, materials, and receptors.[6]

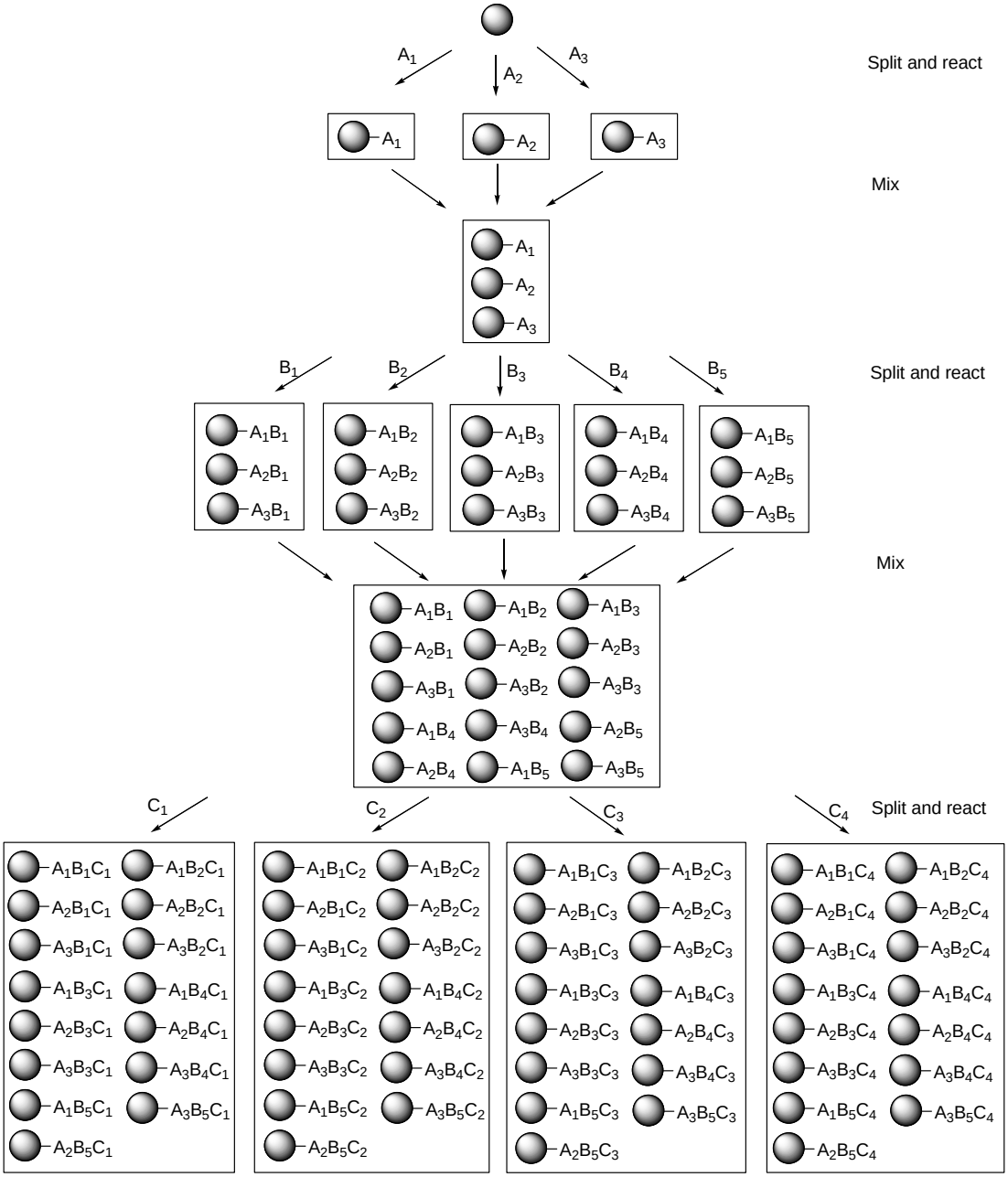
1.1 Combinatorial solid-phase synthesis

The majority of combinatorial libraries synthesis reported in the literature employ solid-phase synthesis, a process in which compounds are synthesized on a heterogeneous polymeric support. The primary advantages of solid-phase synthesis are (i) simple filtration can be used as a separation and purification method, thus eliminating the tedious and time-consuming workup often associated with solution-phase organic synthesis, and (ii) a large excess of reagents may be added to drive the reactions to completion.

Generally, two strategies are used in combinatorial solid-phase synthesis: mix-split synthesis and parallel synthesis.

In mix-split synthesis (Figure 1-1), the starting resin is split into 3 portions and reacted with the first set of reagents (A_1-A_3). After the reaction, the resulting resins are mixed thoroughly and the mixture is split into 5 portions, each consisting of 3 compounds. After the reaction with the second set of reagents (B_1-B_5), a library of 15 different compounds is obtained. The resulting resins are mixed thoroughly and the mixture is split into 4 portions, each consisting of 15 compounds. After the reaction with the third set of reagents (C_1-C_4), a library of 60 different compounds is obtained. The primary advantage of this method is that by executing this mix-split-reaction cycle repetitively, a large library of compounds can be generated. Since the resulting compounds of this method are in a mixture, methods have to be developed for identifying the biologically active components from the mixture. Three approaches are generally used for the structural deconvolution of bioactive compounds from assay data: iterative deconvolution,[4] position scanning deconvolution[7a] and tagging.[7b]

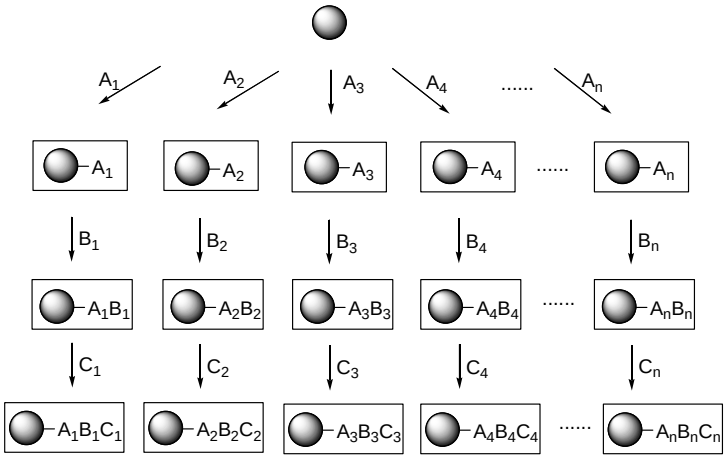
Figure 1-1 Mix-Split Synthesis



Parallel synthesis (Figure 1-2) is a strategy whereby sets of discrete compounds are synthesized in arrays of physically separate reaction vessels or microcompartments without interchange of intermediates during the process. The advantage of this method is that it removes some of the ambiguities associated with pooling compounds. In addition, analytical evaluation of the chemical integrity of the compounds is straightforward. The primary

disadvantage of this method is that the number of compounds that can be synthesized is more limited.

Figure 1-2 Parallel Synthesis



1.1.1 Solid supports in combinatorial solid-phase synthesis

Different types of solid supports ranging from polymers to photolithographic chips to membranes have been used for solid-phase synthesis. As organic reactions could be conducted in various reaction conditions, such as different solvents, temperatures, reagents, and so on, selection of an appropriate solid support is very important in solid-phase synthesis.

1.1.1.1 Polystyrene

The polystyrene supports used for solid-phase synthesis are normally cross-linked by addition of 1-2% divinylbenzene to the polymerization mixture. Polystyrene is presently the most common support material used in solid-phase synthesis because of its good swelling property and high loading. Solvents such as DMF, THF or CH_2Cl_2 swell polystyrene resin while solvents like MeOH, ether, or water shrink it.[8] Merrifield's resin is a divinylbenzene/polystyrene copolymer, which upon chloromethylation yields reactive benzyl chloride functional groups.[8]

1.1.1.2 Tentagel

This is a polystyrene-poly(ethylene glycol) graft copolymer. Compared to polystyrene, Tentagel has better swelling ability in polar solvents, such as water, which makes this support a good alternative in solid-phase synthesis. However its hydroscopic character and chemical instability in strongly basic condition limit its application as a solid support.

1.1.1.3 Polyamide

Various polyamide supports have been developed and these include Pepsyn, which is a copolymer of *N*,*N*-dimethylacrylamide, bis(acrylamidoethane), and *N*-acryloylsarcosine methyl ester,[9a] Pepsyn K, a Kieselguhr supported polyamide which was the first polymeric support used in continuous-flow solid-phase synthesis,[9b] and PolyHIPE, which is prepared by polymerizing polyamide into macroporous polystyrene particles.[10] Each of these polyamide supports has its advantages and disadvantages. For example, Pepsyn has high polarity but low mechanical stability, Pepsyn K has good mechanical stability but low loading capacity and PolyHIPE has higher loading capacity and compatibility with various solvents.

1.1.1.4 Poly(acrylic amide-ethylene glycol) copolymers

This class of polymer includes PEGA, which has a high degree of cross-linking and non-reduced swelling properties, CLEAR which has higher cross-linking and good swelling ability in both polar and non-polar solvents, POEPS and POEPOP which have great chemical and mechanical stability and allow macromolecules such as enzyme to access the interior of the polymer thus allowing the polymer to be used in support-enzyme assays.[11]

1.1.1.5 Inorganic materials

Although organic polymers are the most widely used supports, inorganic materials have also

been reported as supports. Typical examples are controlled pore glass and controlled pore ceramics which were originally used as chromatographic supports. These supports are particularly useful in continuous-flow synthesis and are used in oligonucleotide synthesis. Their loading capacity exceeds that of Pepsyn K.

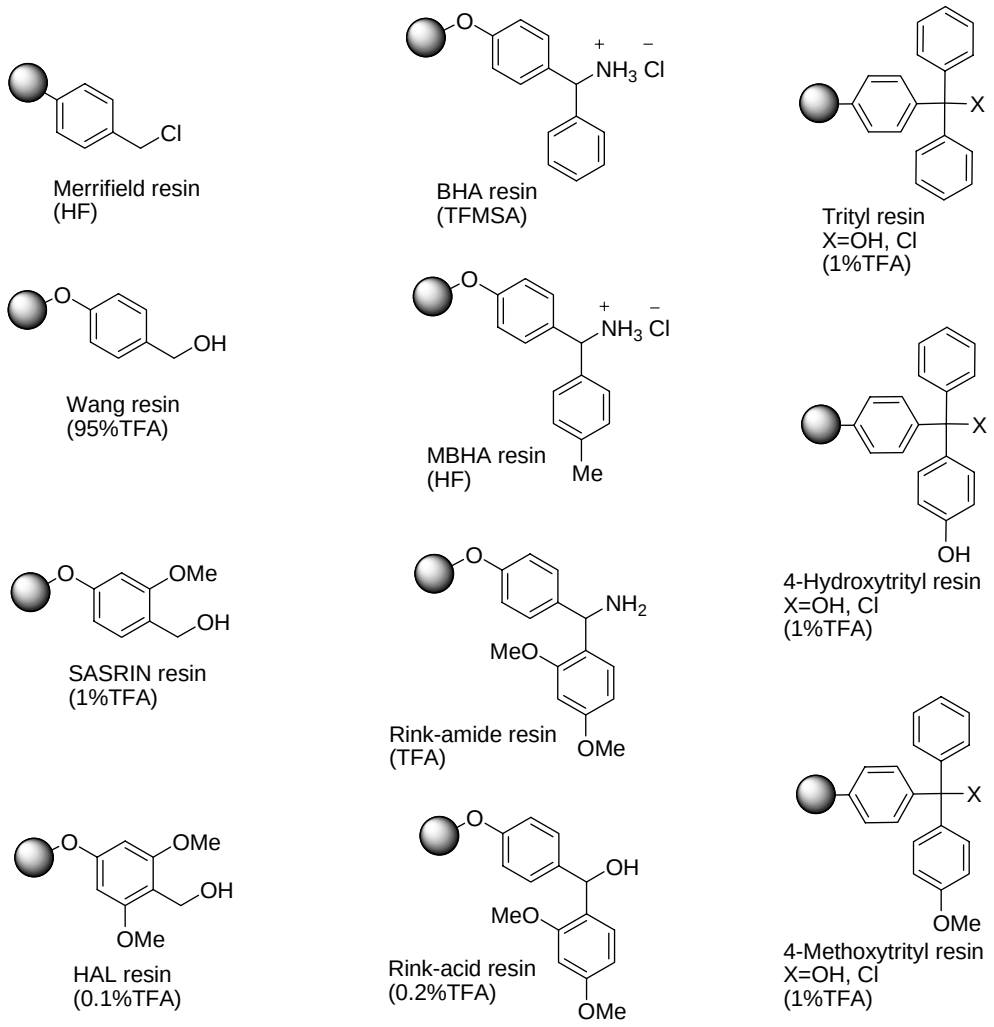
1.1.2 Linkers in combinatorial solid-phase synthesis

A linker is usually a bifunctional molecule that connects the first building block in the solid-phase synthesis to the solid support.[12] The linker must be compatible with all the synthetic steps, yet labile under certain conditions called cleavage, and should have minimum structural and chemical effects on the sought after properties of the synthesized compounds. Therefore choosing the correct linker is a crucial step in combinatorial solid-phase synthesis. Various linkers have been described in the past decades and some of which are described below.

1.1.2.1 Acid-labile linkers

Acid-labile linkers are one of the most common linkers in solid-phase peptide synthesis. They can be classified according to their ability to stabilize the benzylic carbocations generated during cleavage which, in turn, facilitates cleavage of the product from the polymeric support. Figure 1-3 shows the general acid-labile linkers and their acid lability.

Figure 1-3 Acid-Labile Linkers and Their Cleavage



1.1.2.2 Nucleophile-labile linkers

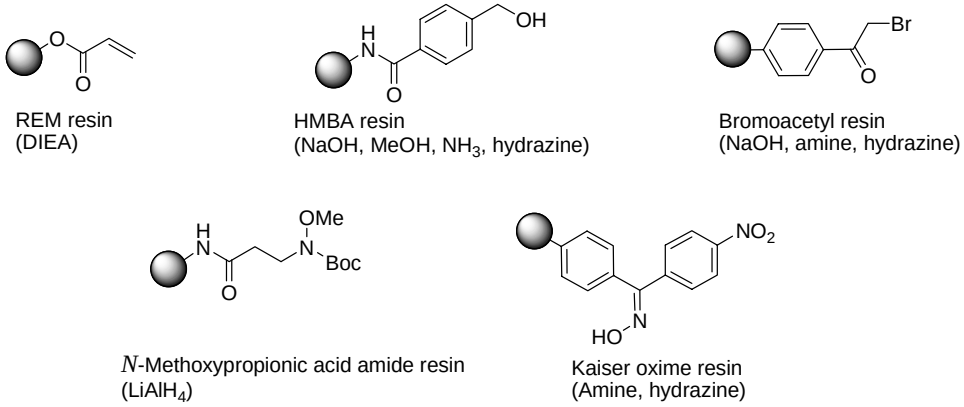
Nucleophile-labile linkers are applicable to the synthesis of target compounds which are unstable or decompose rapidly in acidic condition. When such a linker is used, a nucleophilic displacement occurs during the cleavage step to release the compound from the solid support (Scheme 1-1).

Examples of a nucleophile-labile linker (Figure 1-4) are

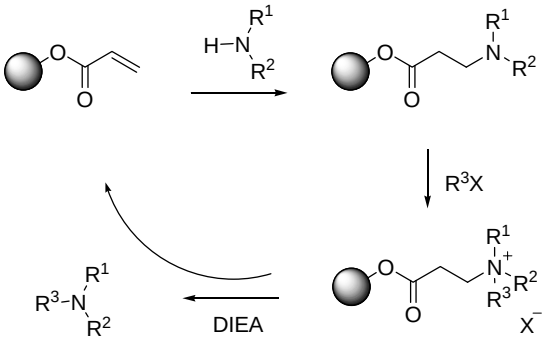
- REM resin, which is compatible with acid and base, and allows the anchoring of primary and secondary amines via Michael addition and releases the tertiary amine as product via Hoffman elimination (Scheme 1-1);[13]

- HMBA and bromoacetyl resins which are stable in strong acids and liberate products by the treatment with NaOH, TEA, NH_3, or hydrazine;
- *N*-methoxypropionic acid amide resin which is used to immobilize carboxylic acids and release them as their corresponding aldehydes by Weinreb's method;[14] and
- Kaiser oxime resin which yields hydrazones, amides or carboxylic acids by cleavage with hydrazine, amine or hydroxypiperidine/Zn/HOAc.

Figure 1-4 Nucleophile-Labile Linkers and Their Cleavage



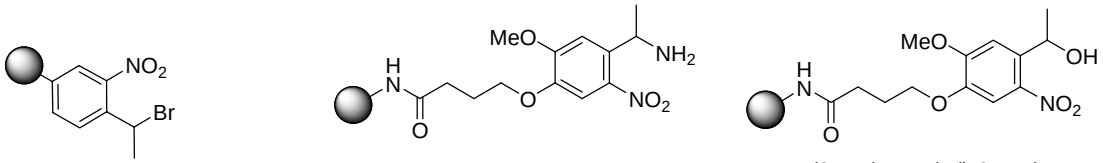
Scheme 1-1 REM Linker in SPS



1.1.2.3 Photo-labile linkers

Unlike traditional cleavage which employs chemical reagents, photo-labile anchors release products by irradiation at λ = 320-365 nm. This cleavage can be carried out in aqueous solution which makes this approach particularly useful for biological assays (Scheme 1-2).[15] Examples of photo-labile resins are shown in Figure 1-5.

Figure 1-5 Photo-Labile Linkers

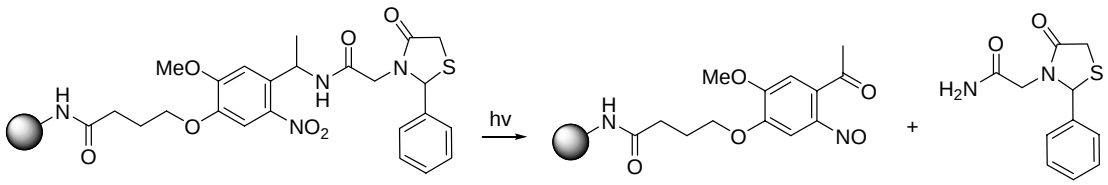


1-Bromoethyl-3-nitrophenyl resin

4-(2-Aminoethyl)-2-methoxy-5-nitrophenoxy resin

4-(2-Hydroxyethyl)-2-methoxy-5-nitrophenoxy resin

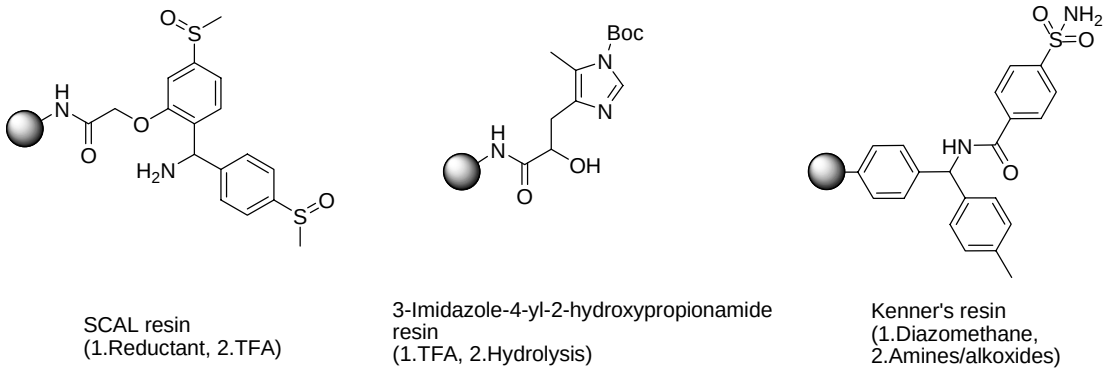
Scheme 1-2 Cleavage of a Photo-Labile Linker in SPS



1.1.2.4 Safety-catch linkers

The cleavage of safety-catch linkers involves two steps - the first step is a reaction that activates the secured product into a cleavable stage, whilst the second step liberates the product (Scheme 1-3). Many safety-catch linkers have been developed in solid-phase synthesis and three of them are shown in Figure 1-6. For example, Kenner's safety-catch resin is stable to most nucleophiles before activation but becomes susceptible after activation with diazomethane or iodoacetonitrile. Treating the activated resin with amines or alkoxides generates the corresponding amides or esters (Scheme 1-3).[16]

Figure 1-6 Safety-Catch Linkers and Their Cleavage

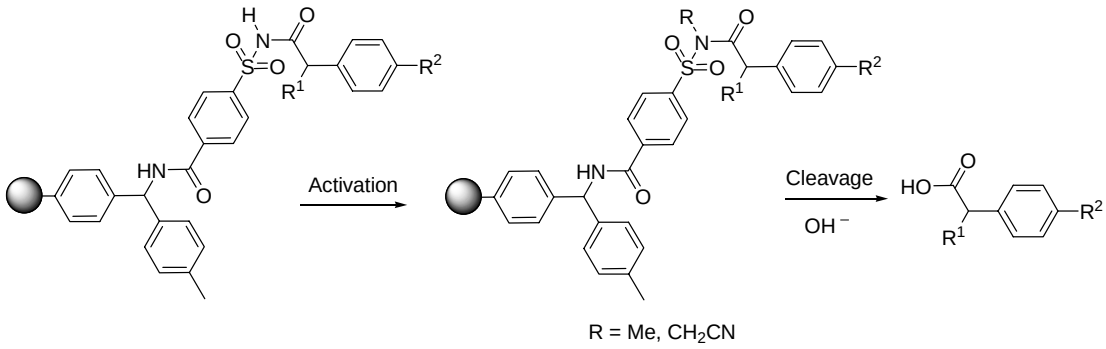


SCAL resin
(1.Reductant, 2.TFA)

3-Imidazole-4-yl-2-hydroxypropionamide resin
(1.TFA, 2.Hydrolysis)

Kenner's resin
(1.Diazomethane, 2.Amines/alkoxides)

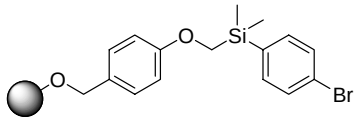
Scheme 1-3 Cleavage of Kenner's Safety-Catch Linker in SPS



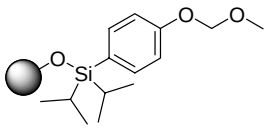
1.1.2.5 Traceless linkers

Traceless linkers release products in a way such that no trace or memory of the solid-phase synthesis can be observed.[17a] Such linkers are highly desirable as they minimize the effects of residual functionality on the synthesized compounds. The most widely exploited class of these linkers is based on silicon chemistry (Figure 1-7). Their cleavage is often achieved by fluoride salts or by ipso-substitution with C-H, C-I, C-Br at the Si-C bond.[17a] Scheme 1-4 shows one example of silicon-based traceless linker in SPS.[17b,17c]

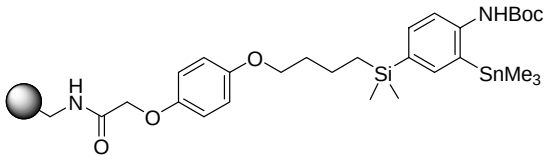
Figure 1-7 Silicon-Based Traceless Linkers and Their Cleavage



4-(4-(Hydroxymethyl)-phenoxymethyl-dimethylsilyl)-bromobenzene resin
(TFA, CsF)

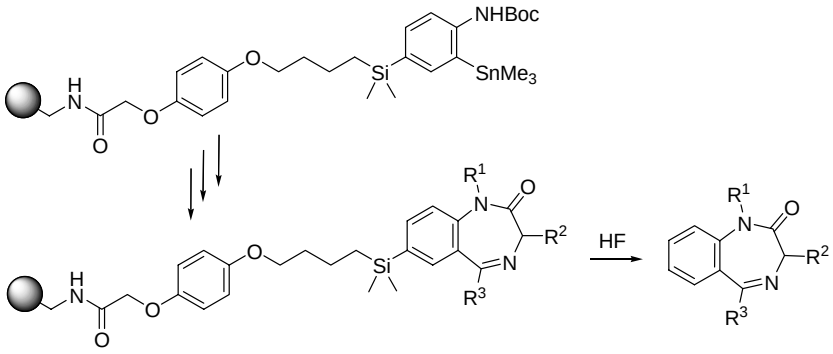


4-Methoxymethyl-oxyphenyl-diisopropylhydroxysilyl resin
(TBAF)



tert-Butyl 4-(dimethyl(4-(4-(2-(methylamino)-2-oxoethoxy)phenoxy)butyl)silyl)-2-(trimethylstannyl)phenylcarbamate resin
(TFA, H_2O, Me_2S)

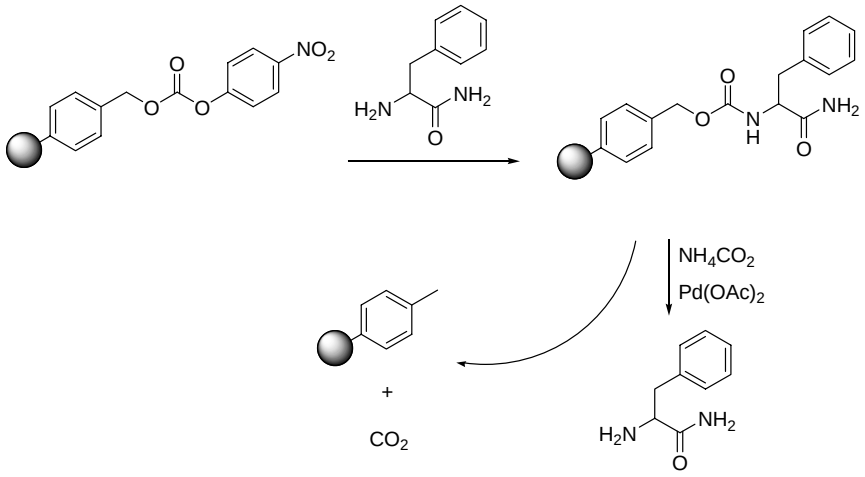
Scheme 1-4 Cleavage of a Silicon-Based Traceless Linker in SPS



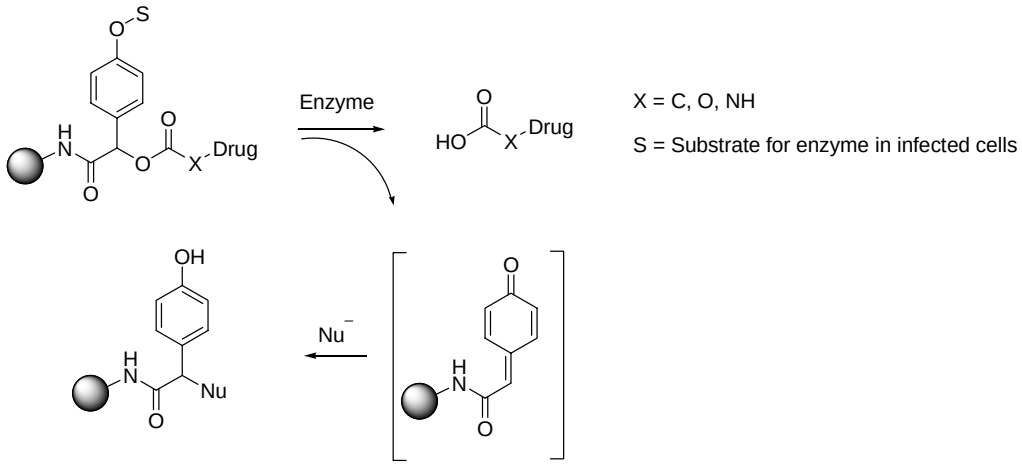
1.1.2.6 Other linkers

Besides the aforementioned linkers, some other linkers release products via special cleavage conditions, for example, hydrogenolysis with hydrogen or ammonium formate in the presence of $Pd(OAc)_2$ (Scheme 1-5)[18] or enzyme promoted cleavage (Scheme 1-6).[19] The specificity of enzyme enables products to be released in a highly selective manner such that no other parts of the synthesized compounds will be altered.

Scheme 1-5 Cleavage by Hydrogenolysis



Scheme 1-6 Enzyme Promoted Cleavage in SPS



1.1.3 Analytical methods in solid-phase synthesis

Organic reactions on solid-phase require different monitoring and analytical methods from solution-phase due to the solid support's insolubility in solvents. Thus many on-support analytical techniques have been developed and used for the characterizations of substrates on solid supports.

1.1.3.1 FTIR method

The most widely used on-support characterization technique for the monitoring of solid-phase

synthesis is FTIR. It provides qualitative analysis of solid bound substrates. In particular, single bead FTIR microspectroscopy technique which performs a non-destructive analysis on a single bead is advantageous as it contains both sensitivity and speed.[20]

1.1.3.2 Gel-phase NMR

Due to the restricted mobility and the magnetically inhomogeneous environment throughout the substrate, the NMR spectra of solid-supported substrates appear as broad lines which does not allow for meaningful analysis. To circumvent this problem, gel-phase NMR was introduced and this involves analyzing solvent swollen resins with a standard liquid NMR probe. In gel-phase NMR, the resin is allowed to swell in a solvent so as to provide the molecules with a greater degree of mobility. This helps in narrowing the NMR spectra to a limited extent and is thus practical only for nuclei with a large chemical shift range (e.g., ^{13}C, ^{19}F, ^{31}P NMR).

1.1.3.3 High-resolution magic angle spinning (HR-MAS) NMR

As proton NMR spectra are crucial in reaction monitoring and structure elucidation, HR-MAS NMR technique is used to solve the line-broadening problem in proton NMR. It requires the use of a high resolution MAS probe which allows the magnetic susceptibility-induced line broadening terms to average out by a special angle spinning. HR-MAS NMR technique is a useful tool in resin-bound substrates characterization.

1.1.3.4 Spectrophotometric methods

Spectrophotometric methods have been developed for the analysis of solid-phase peptide synthesis. By using molecular markers that react specifically with a functional group, together with UV-visible or fluorescence spectroscopy, quantitative analysis of aldehyde, ketone,

hydroxyl and carboxy groups has been done.[21]

1.2 Combinatorial solution-phase synthesis

The concept of combinatorial chemistry is often associated with solid-phase synthesis, which offers many advantages for easy and reliable combinatorial libraries generation. Nevertheless, a significant amount of combinatorial efforts have also been done by solution-phase work. The selection of combinatorial synthesis strategy is determined by many factors such as (i) the purpose of the synthesis, i.e., is it for lead discovery or lead optimization, (ii) the format of screen, and (iii) the required purity of the final compounds. Unlike solid-phase synthesis, solution-phase synthesis does not require the design and development of a strategy for the attachment and cleavage of a substrate from the solid support. This simplification, as well as the maturity of solution-phase chemistry, shortens the synthesis time.

1.2.1 Combinatorial solution-phase pool synthesis

This strategy prepares libraries of target compounds in mixtures, which is useful for the quick identification of the most biologically active compounds from libraries. The first example was described by a group from Glaxo who synthesized a total of 1600 amides and esters from 40 acid chlorides with 40 amines and alcohols.[22] In their experiment, two libraries were prepared. In each pool of the first library, a single acid chloride was reacted with an equal molar mixture of amines and alcohols, and 40 pools with each pool containing 40 compounds were prepared. In each pool of the second library, a single amine or alcohol was reacted with an equal molar mixture of acid chlorides and 40 pools were also prepared. Subsequently the libraries were screened for biological activity in a pool identified manner to find the most active amide or

ester.

1.2.2 Combinatorial solution-phase parallel synthesis

Compared to combinatorial solution-phase pool synthesis, parallel synthesis which gives products as individual component is less frequently used for large library generation.

However, Watson and his coworkers have reported a single step synthesis for the generation of a modest library of 20 discrete 2-amino-thiazoles using this methodology.[23] In their experiment, 5 primary thioureas were reacted with 4 α-bromoketones in DMF to give 2-aminothiazoles. The reaction tolerated the presence of both acidic and basic functionalities on the reactants without protection, and the products did not require purification.

Additionally, a few research groups have reported using solution-phase parallel synthesis for multi-component reactions. One example involves the Ugi reaction which is a one-pot, four-component condensation reaction for the synthesis of α-acylaminoamide. Weber has reported the preparation of 20 libraries, each containing 20 individual Ugi products, which were tested for thrombin-inhibitory activity.[24a] Similar work on this reaction was also conducted by Keating.[24b]

1.3 Objectives of our studies

As mentioned earlier, combinatorial synthesis plays a very important role in the drug discovery process. Since peptides and oligonucleotides are problematic for drug development because their oral bioavailability is poor and they are degraded rapidly by enzymes, the focus of combinatorial research has shifted in recent years to libraries of nonpolymeric small molecules having molecular weights of about 500 daltons or less.[25] Thus, one of the purposes

of this project is to investigate the combinatorial synthesis of small *N*-heterocycles. In particular, we plan to:

1) develop solid-phase synthetic routes to xanthines and pyrazolidine-3,5-diones, and prepare representative sets of these compounds using a combinatorial solid-phase parallel synthesis strategy, and

2) develop a solution-phase synthetic route to polycyclic guanines, and prepare representative sets of polycyclic guanines using a combinatorial solution-phase parallel synthesis strategy.

The advantages of solid-phase reactions could be combined with the benefits of solution phase chemistry through the use of polymer-supported reagents. In the second part of this project, we intend to develop a polymer-supported Hantzsch ester and examine its application as a polymeric reductant.

1.4 References

[1] Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154.

[2] Houghten, R. A. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 5131-5135.

[3] Furka, A.; Sebestyen, F.; Asgedom, M.; Dibo, G. *Abstr. 14th Int. Congr. Biochem.* **1988**, *5*, 47.

[4] Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H. *Nature* **1991**, *354*, 84-86.

[5] Lam, K. S.; Salmon, S. E.; Hersch, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J. *Nature* **1991**, *354*, 82-84.

[6] Czarnik, A. W.; Dewitt, S. H. *A Practical Guide to Combinatorial Chemistry.* American Chemical Society, Washington, DC, 1997.

[7] (a) Pinilla, C.; Appel, J. R.; Blanc, P.; Houghten, R. A. *Biotechniques* **1992**, *13*, 901-905. (b) Janda, K. D. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 10779-10785.

[8] Bayer, E. *Angew. Chem.* **1991**, *103*, 117-133.

[9] (a) Atherton, E.; Brown, E.; Sheppard, R. C.; Rosevear, A. *J. Chem. Soc., Chem. Commun.* **1981**, 1151-1152. (b) Arshady, R.; Atherton, E.; Clive, D. L. J.; Sheppard, R. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, *1*, 529-538.

[10] (a) Small, P. W.; Sherrington, D. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1589-1591. (b) Raillard, S. P.; Ji, G.; Mann, A. D.; Baer, A. *Org. Process Res. Dev.* **1999**, 3, 177-183. (c) Yang, R.-Y.; Kaplan, A. *Tetrahedron Lett.* **2000**, *41*, 7005-7008. (d) Yang, R.-Y.; Kaplan, A. *Tetrahedron Lett.* **2001**, *42*, 4433-4435. (e) Lipshutz, B. H.; Blomgren, P. A. *Org. Lett.* **2001**, *3*, 1869-1871.

[11] Renil, M.; Meldal, M. *Tetrahedron Lett.* **1996**, *37*, 6185-6188.

[12] Fenniri, H. *Combinatorial Chemistry, A Practical Approach.* Oxford University Press: Oxford, New York, 2000.

[13] (a) Morphy, J. R.; Rankovic, Z.; Rees, D. C. *Tetrahedron Lett.* **1996**, *37*, 3209-3212. (b) Brown, A. R.; Rees, D. C.; Rankovic, Z.; Morphy, J. R. *J. Am. Chem. Soc.* **1997**, *119*, 3288-3295. (c) Caix-Haumesser, S.; Hanna, I.; Lallemand, J. -Y.; Peyronel, J. -F. *Tetrahedron Lett.* **2001**, *42*, 3721-3723. (d) Winkler, J. D.; Kwak, Y. -S. *J. Org. Chem.* **1998**, *63*, 8634-8635.

[14] Mutter, M.; Bellof, D. *Helv. Chim. Acta* **1984**, *67*, 2009-2016.

[15] Holmes, C. P.; Jones, D. G. *J. Org. Chem.* **1995**, *60*, 2318-2319.

[16] (a) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171-11172. (b) Backes, B. J.; Virgilio, A. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 3055-3056. (c) Golisade, A.; Herforth, C.; Wieking, K.; Kunick, C.; Link, A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1783-1786. (d) Ingenito, R.; Bianchi, E.; Fattori, D.; Pessi, A. *J. Am. Chem. Soc.* **1999**, *121*, 11369-11374.

[17] (a) Gordon, K.; Balasubramanian, S. *J. Chem. Technol. Biotechnol.* **1999**, *74*, 835-851. (b) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 6006-6007. (c) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 2885-2893.

[18] Pande, C. S.; Gupta, N.; Bhardwaj, A. *J. Appl. Polym. Sci.* **1995**, *56*, 1127-1131.

[19] Lee, M.-R.; Baek, K.-H.; Jin, H.-J; Jung, Y.-G.; Shin, I. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 1675-1678.

[20] (a) Yan, B.; Kumaravel, G. *Tetrahedron* **1996**, *52*, 843-848. (b) Yan, B.; Kumaravel, B.; Anjaria, H.; Wu, A.; Petter, R. C.; Jewell, C. F.; Wareinget, J. J. R. *J. Org. Chem.*

1995, *60*, 5736-5738.

[21] (a) Yan, B.; Li, W. *J. Org. Chem.* **1997**, *62*, 9354-9357. (b) Yan, B.; Liu, L.; Astor, C. A.; Tang, Q. *Anal. Chem.* **1999**, *71*, 4564-4571.

[22] Smith, P. W.; Lai, J. Y. Q.; Whittington, A. R.; Cox, B.; Houston, J. G.; Stylli, C. H.; Banks, M. N.; Tiller, P. R. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2821-2824.

[23] Bailey, N., Dean, A. W.; Judd, D. B.; Middlemiss, D.; Storer, R.; Watson, S. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1409-1414.

[24] (a) Weber, L.; Wallbaum, S.; Broger, C.; Gubernator, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2280-2282. (b) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 7842-7843.

[25] Dolle, R. E. *J. Comb. Chem.* **2005**, *7*, 739-798.

Chapter 2 Combinatorial Solid-Phase Synthesis of Xanthines

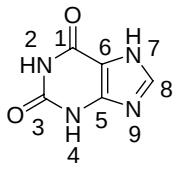
2.1 Introduction

2.1.1 Importance of xanthines

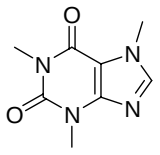
Xanthines constitute an important class of pharmacologically active compounds which are commonly used for their effects as mild stimulants, bronchodilators, phosphodiesterase inhibitors, CFTR chloride channel activators and adenosine receptor antagonists.[1] In recent years, the spectrum of clinical applications of xanthines has continued to widen and presently include their use as anticonvulsants,[2] nootropics,[3] and therapeutics for the treatment of migraine headaches and illnesses where under-activation of the HM74A receptor contributes to the disease.[4]

There are many drugs that are xanthine derivatives (Figure 2-1). These include caffeine, which is the most popular psychostimulant drug in the world; theophylline, an anti-asthmatic drug; lisofylline, an experimental anti-inflammatory drug; and so on.

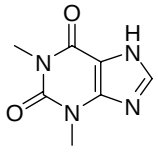
Figure 2-1 Structures of Xanthine and Its Derivatives



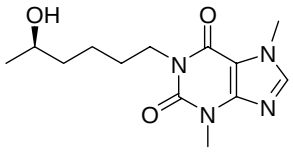
Xanthine



Caffeine



Theophylline

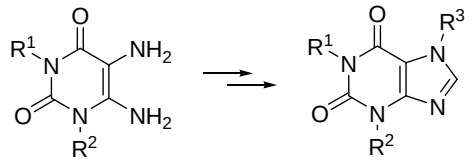


Lisofylline

2.1.2 General methods for solution-phase synthesis of xanthines

The first solution-phase synthetic method to the preparation of xanthine was reported by W. Traube[5] in 1900. Since then, other synthetic methods have been developed.[6] Most of these methods employed substituted 5,6-diamino uracil as the key precursor for the xanthine formation (Scheme 2-1). In this classical method, substituents R^1 and R^2 are introduced in the early stages of the synthesis, which requires that nearly the entire synthesis had to be repeated for each combination of R^1 and R^2. Additionally, the reactions for the formation of the 5-membered ring were either harsh, had long reaction times, required non-readily accessible reagents, or involved a tedious workup.[7] These disadvantages made this method less useful in modern synthetic organic chemistry, especially in combinatorial chemistry.

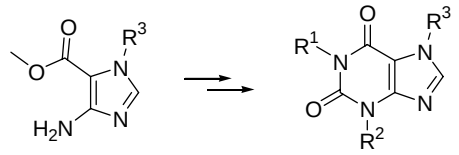
Scheme 2-1 Synthesis of Xanthines via 5,6-Diamino Uracil



5,6-Diamino uracil Xanthine

An alternative method for the preparation of xanthines involves the cyclocondensation of 4-amino-5-alkoxycarbonylimidazole.[6a,6d,6e] In this synthetic strategy, the 5-membered ring is built prior to the 6-membered ring (Scheme 2-2). We felt that this was a more attractive method than the one described earlier as it allows the N1 and N3 substituents to be introduced later in the synthesis, thus avoiding the need to repeat almost the entire synthesis for each combination of N1 and N3 substituents.

Scheme 2-2 Synthesis of Xanthines via Imidazole

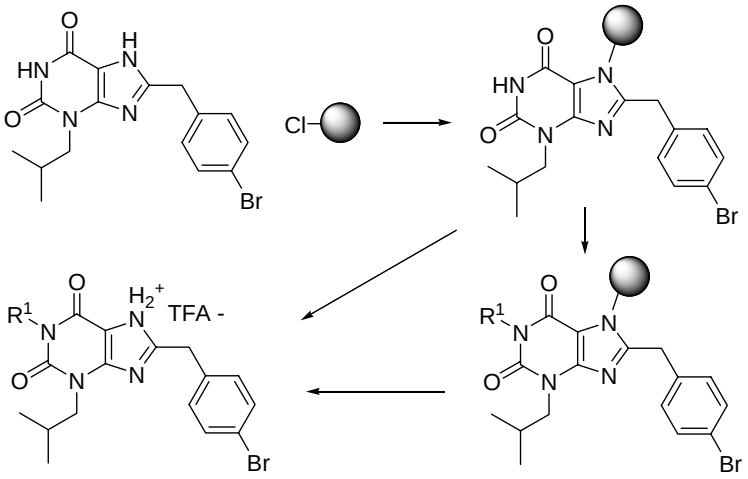


4-Amino-5-alkoxycarbonylimidazole Xanthine

2.1.3 Objectives and scope of this study

As mentioned earlier, numerous solution-phase routes for the synthesis of xanthines have been developed. However, to the best of our knowledge, the only solid-phase procedure reported to-date involves the derivatization of a xanthine scaffold (Scheme 2-3).[8]

Scheme 2-3 Derivatization of Xanthine Using a Solid Support



Since the solid-phase synthesis of xanthines is not well-explored, this project aims to develop solid-phase synthetic methodologies to this class of compounds. In this project, we plan to:

1) design and develop solid-phase synthetic routes to xanthines,

2) optimize the reaction conditions for each step of the reaction, and

3) prepare representative sets of xanthines using these solid-phase synthesis methodologies to illustrate its versatility.

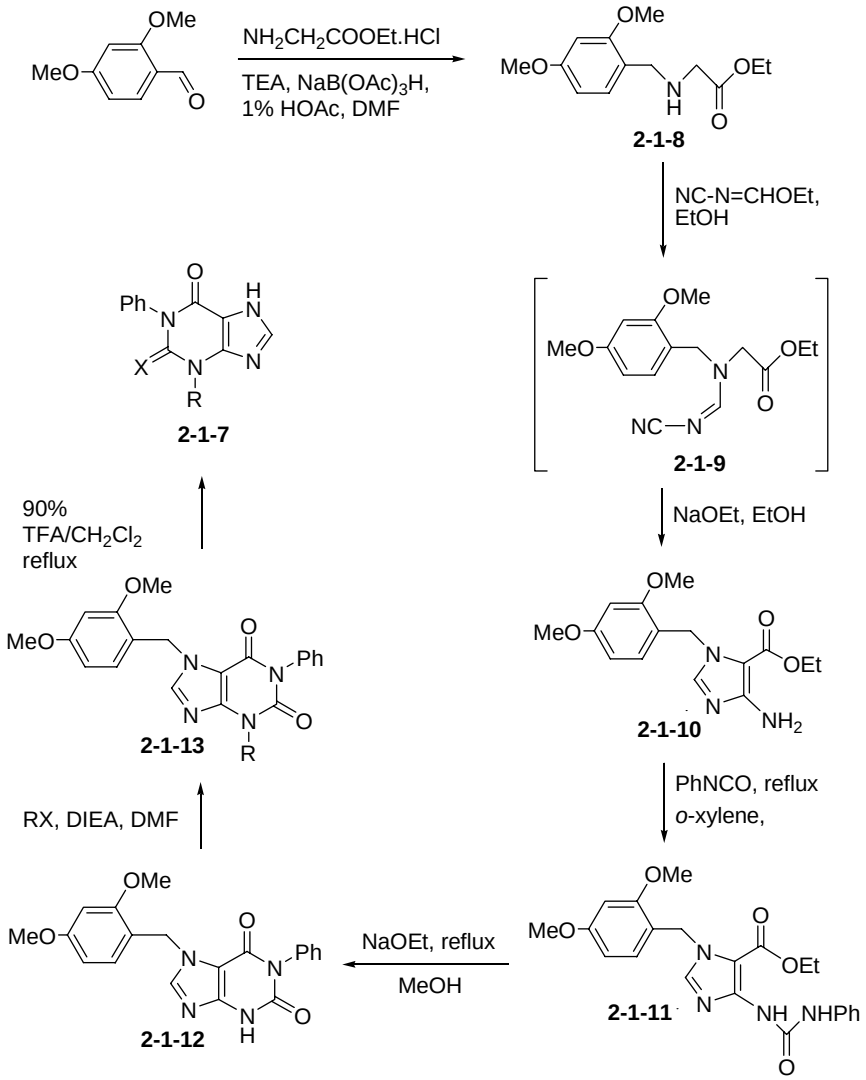
2.2 Results and Discussion

2.2.1 Solid-phase synthesis of 1,3-substituted xanthines

2.2.1.1 Solution-phase synthesis of 1,3-substituted xanthines

Prior to solid-phase synthesis, preliminary solution-phase studies (Scheme 2-4) were carried out to survey the required reaction conditions and establish the conditions required for solid-phase synthesis.

Scheme 2-4 Solution-Phase Synthesis of 1,3-Substituted Xanthines



2.2.1.1.1 Synthesis of ethyl *N*-(2,4-dimethoxybenzyl) glycinate (2-1-8)

To begin our investigation, ethyl *N*-(2,4-dimethoxybenzyl) glycinate **2-1-8** was prepared by

reductively alkylating 2,4-dimethoxybenzaldehyde (a mimic of the PS-MB-CHO resin) with ethyl glycinate. Attempts to carry out the reaction with $NaBH_4$/EtOH,[9a] $NaB(OAc)_3H$/NaOAc/MeOH[9b] or $NaB(OAc)_3H$/DMF gave yields of 20-63% which were not optimal for solid-phase synthesis. Further experimentation eventually provided $NaB(OAc)_3H$/1% HOAc/DMF, which gave **2-1-8** in 95% yield, and no improvement was observed when more HOAc was added to the reaction system (Table 2-1).

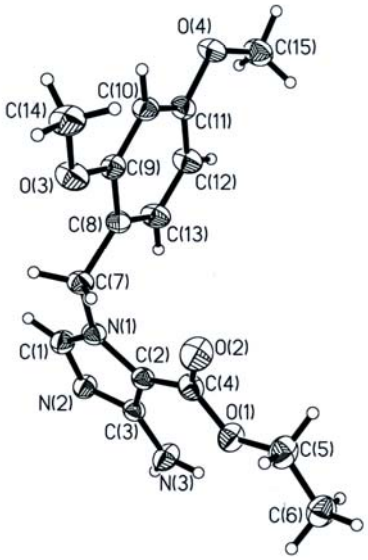
Table 2-1 Synthesis of **2-1-8**

Entry	*Reagent and solvent*	*Conditions*	*Result*
1	$NaBH_4$/EtOH	rt, 24 h	20% yield
2	$NaB(OAc)_3H$/NaOAc/MeOH	rt, 96 h	63% yield
3	$NaB(OAc)_3H$/DMF	rt, 72 h	57% yield
4	$NaB(OAc)_3H$/1% HOAc/DMF	rt, 8 h	95% yield

2.2.1.1.2 Synthesis of ethyl 5-amino-3-(2,4-dimethoxybenzyl)-3*H*-imidazole-4-carboxylate (2-1-10)

Subsequently **2-1-8** was treated with ethoxymethylene cyanamide using a slightly modified form of the procedure described by Asberom *et al*,[10] to give the intermediate **2-1-9**, which was cyclized with NaOEt in an one-pot reaction to give **2-1-10** in 70% overall yield. We realized that to obtain higher yields, it was essential to keep the reaction mixture at low temperature during the addition of NaOEt. The X-ray structure of **2-1-10** was obtained and is shown in Figure 2-2.

Figure 2-2 X-Ray Structure of **2-1-10**



2.2.1.1.3 Synthesis of ethyl 3-(2,4-dimethoxybenzyl)-5-(3-phenylureido)-3*H*-imidazole-4-carboxylate (2-1-11)

Treatment of **2-1-10** with phenyl isocyanate in *o*-xylene (120 °C, 8 h) provided **2-1-11** in 90% yield. However when **2-1-10** was reacted with isothiocyanates, the reaction mixtures had to be heated in *o*-xylene at 140 °C for 24 h to give the products in 83% yield and traces of unreacted **2-1-10**. Attempts to drive the reaction to completion by prolonging the heating time, addition of a base as a catalyst[11] or using microwave irradiation proved futile.

2.2.1.1.4 Synthesis of 7-(2,4-dimethoxybenzyl)-1-phenylxanthine (2-1-12)

Subsequent ring closure of **2-1-11** with NaOEt/MeOH afforded 1-substituted xanthine **2-1-12** in quantitative yield. Since MeOH was not a good solvent for the swelling of a polystyrene resin (a required condition for solid-phase synthesis), we therefore repeated the reaction with

a MeOH-THF mixture and were gratified to obtain the same result. In this reaction, an acid-base workup was sufficient to obtain the product in high purity. This greatly simplified the purification step.

2.2.1.1.5 Synthesis of 7-(2,4-dimethoxybenzyl)-1-phenyl-3-substitutedxanthine (2-1-13)

To obtain 1,3-substituted xanthines, **2-1-12** was treated with various alkyl halides in DMF under basic conditions. The reaction proceeded readily at rt to provide **2-1-13** in good yields (Table 2-2).

Table 2-2 Synthesis of **2-1-13**

Entry	*Alkylating reagent*	*Base and Solvent*	*Conditions*	*Result*
1	CH_3I	DIEA/DMF	rt, 0.5 h	92% yield
2	BnBr	DIEA/DMF	rt, 4 h	88% yield
3	BuI	DIEA/DMF	rt, 24 h	70% yield
4	Propargyl bromide	DIEA/DMF	rt, 1 h	90% yield

2.2.1.1.6 Synthesis of 3-methyl-1-phenylxanthine (2-1-7b)

Removal of the 2,4-dimethoxybenzyl moiety was achieved by refluxing **2-1-13** in 90% TFA/ CH_2Cl_2. Using lower concentrations of TFA in CH_2Cl_2 (such as 30%, 50% and 70%) also worked well but longer reaction times were needed (Table 2-3).

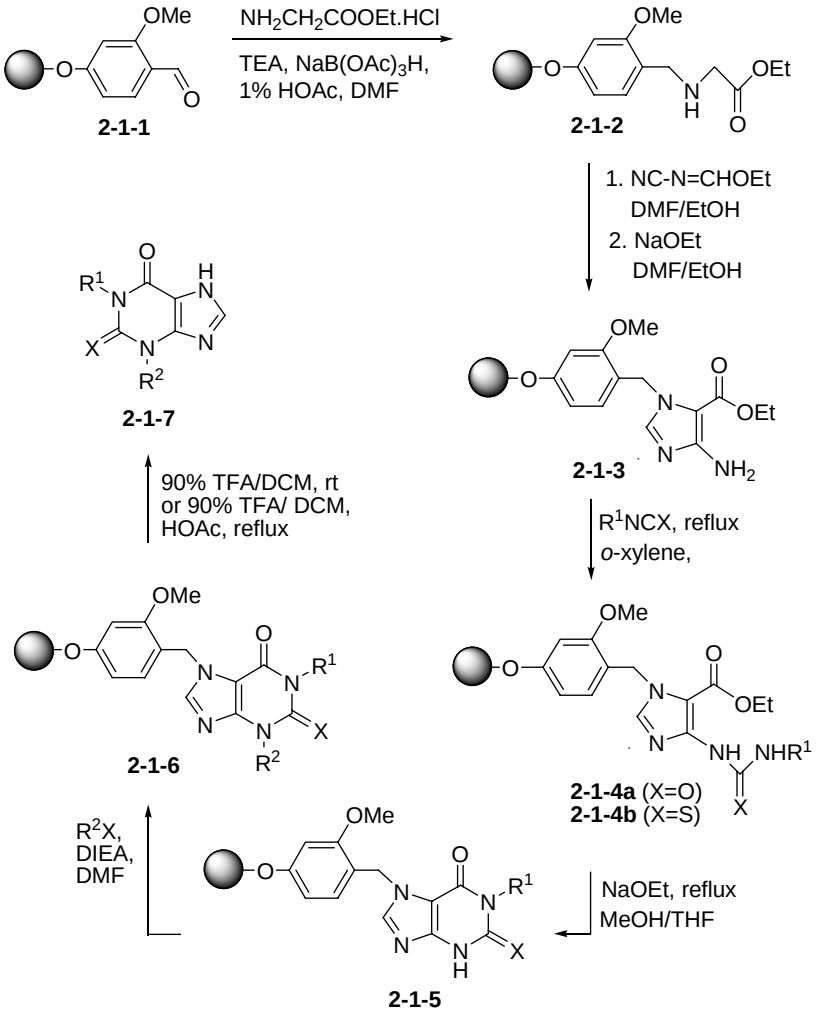
Table 2-3 Synthesis of **2-1-7b**

Entry	*Reagent*	*Conditions*	*Result*
1	30% TFA in CH_2Cl_2	60-70 °C	Reaction completed in 6 h
2	50% TFA in CH_2Cl_2	60-70 °C	Reaction completed in 5 h
3	70% TFA in CH_2Cl_2	60-70 °C	Reaction completed in 3 h
4	90% TFA in CH_2Cl_2	60-70 °C	Reaction completed in 1 h

2.2.1.2 Solid-phase synthesis of 1,3-substituted xanthines

With the solution-phase pathway established, we proceeded to adapt the methodology to solid-phase synthesis (Scheme 2-5).

Scheme 2-5 SPS of 1,3-Substituted Xanthines



To facilitate the solid-phase synthesis of 4-amino-5-alkoxycarbonylimidazole, we required ready access to multigram quantities of CHO resin. Amongst the CHO functionalized resins available, the ArgoGel-MB-CHO or ArgoPore-MB-CHO resins are commonly used for solid-phase reactions due to their good swelling property in most organic solvents.[12] However these resins are highly expensive, which limits their potential use on a large scale. The PS-MB-CHO resin **2-1-1** is a cheaper resin, but it has rarely been used in solid-phase synthesis due to

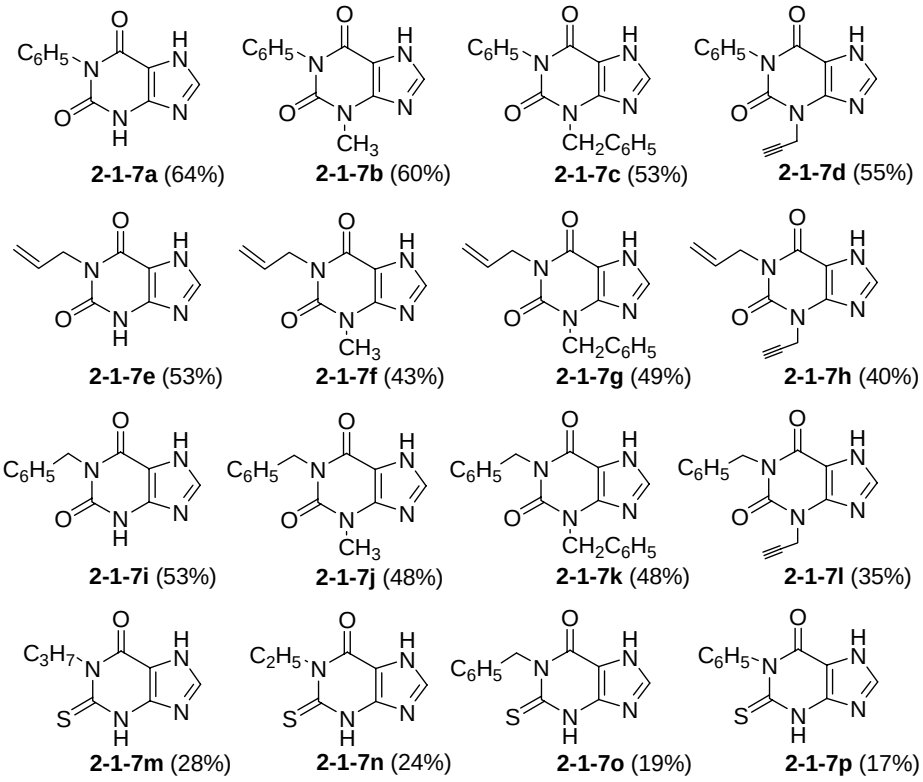
its poor swelling in some solvents. We figured that by circumventing this problem, wider applicability could be achieved for resin **2-1-1**.

Resin **2-1-1** was converted to **2-1-2** by reductive amination in DMF. The formation of **2-1-2** was amenable to KBr FTIR monitoring (*i.e.* disappearance of the CH stretch of aldehyde at 2763 cm^{-1} and the shift of the C=O stretch at 1681 cm^{-1} to 1737 cm^{-1}, indicating the presence of an ester). Due to the poor swelling ability of polystyrene/1% divinylbenzene in EtOH, treatment of **2-1-2** with ethoxymethylene cyanamide was carried out in a DMF/EtOH (v/v 1:2) mixture. This was followed by the addition of NaOEt/EtOH to afford the polymer-supported 4-amino-5-ethoxycarbonylimidazole **2-1-3**. Treatment of **2-1-3** with various isocyanates in *o*-xylene (120 °C, 24 h) provided **2-1-4a**, which was cyclized using NaOEt in MeOH/THF (v/v 1:4) to give **2-1-5**. The N1 substituted xanthines could be released from the solid support with 90% TFA/CH_2Cl_2 at rt or they could be treated with alkyl halides in DIEA/DMF to afford **2-1-6**. To illustrate the versatility of this chemistry, a small library of 12 compounds (**2-1-7a - 2-1-7l**) was prepared (Figure 2-3). The overall yields obtained were 35-64% (purities of > 95% by NMR) indicating an average yield of 86-93% for each step of the SPS.

We have also examined the application of this methodology for the synthesis of thioxanthines. Due to the lower reactivity of isothiocyanates, formation of **2-1-4b** was carried out at 140 °C and by iterating this procedure 3 times, the yield was increased more than four-fold. Cleavage of **2-1-5** from the support with 90% TFA/CH_2Cl_2 at rt liberated products which did not correspond to the desired substituted thioxanthines (**2-1-7m - 2-1-7p**) whilst treatment with refluxing glacial acetic acid gave a mixture of **2-1-7** and byproducts. Hence, to simplify the purification of **2-1-7**, a two-step cleavage procedure was used: the resin was first treated with

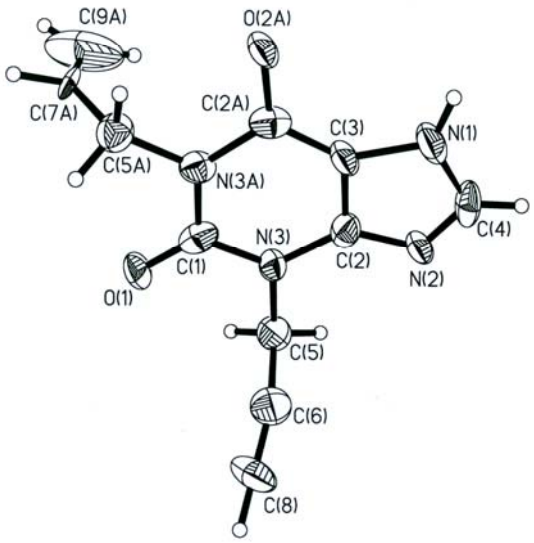
90% TFA/CH_2Cl_2 at rt to detach the byproducts before liberating the thioxanthines with refluxing glacial acetic acid. By using this novel solid-phase synthesis methodology, a representative set of 4 thioxanthines was prepared (Figure 2-3) in acceptable overall yields and purities.

Figure 2-3 Library of 1,3-Substituted Xanthines **2-1-7**



To illustrate the structure of xanthine derivatives, an X-ray structure of compound **2-1-7h** was obtained and is shown in Figure 2-4.

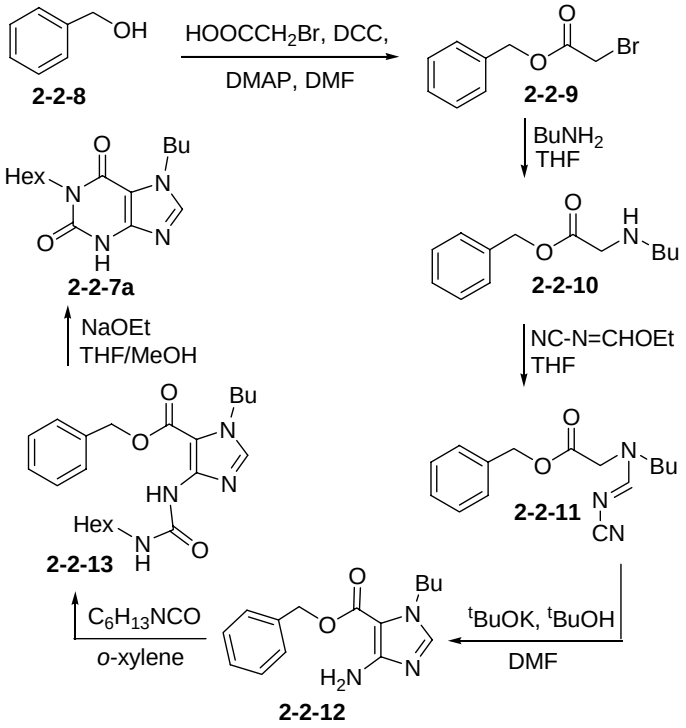
Figure 2-4 X-Ray Structure of **2-1-7h**



2.2.2 Traceless solid-phase synthesis of substituted xanthines

2.2.2.1 Solution-phase synthesis of substituted xanthines

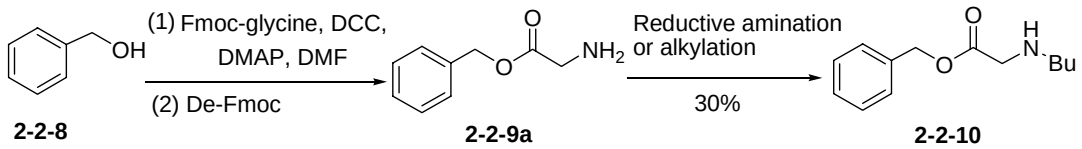
Scheme 2-6 Solution-Phase Synthesis of Substituted Xanthines



2.2.2.1.1 Synthesis of benzyl *N*-butyl glycinate (2-2-10)

To begin our investigation, we had to prepare benzyl *N*-substituted glycinate **2-2-10** which was initially achieved by coupling benzyl alcohol **2-1-8** with Fmoc-glycine followed by Fmoc-deprotection and reductive amination or alkylation (Scheme 2-7). The yield obtained was only 30% which was unacceptable for application in solid-phase synthesis.

Scheme 2-7 Synthesis of **2-2-10**



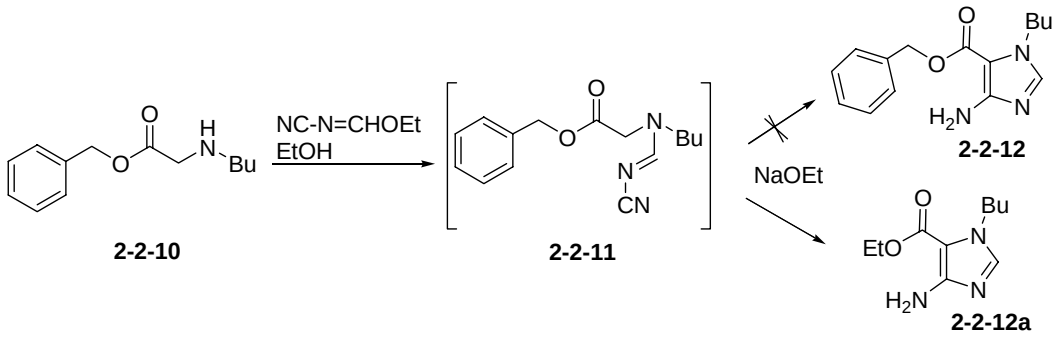
Further experimentation showed that **2-2-10** could be obtained more expediently and in better yields by reacting **2-2-8** with bromoacetic acid to give **2-2-9** which, in turn, could be

efficiently treated with butylamine in THF to provide **2-2-10** in 75% overall yield. Good yields can also be achieved by reacting **2-2-9** with benzylamine and methylamine.

2.2.2.1.2 Synthesis of benzyl 2-(*N*-butyl-*N'*-cyanoformamidino)acetate (2-2-11)

Treatment of **2-2-10** with ethoxymethylene cyanamide gave intermediate **2-2-11** which upon reaction with NaOEt in anhydrous EtOH underwent rapid imidazole ring formation.[6] However ^{1}H NMR data of the product obtained showed that the benzyl group had been replaced by an ethyl moiety (Scheme 2-8) which meant the procedure could not be applied to a solid-phase format. Attempts to lower the reaction temperature to 0 °C did not prevent the loss of the benzyl moiety and at -30 °C, the cyclization reaction ceased to proceed.

Scheme 2-8 Synthesis of **2-2-12**

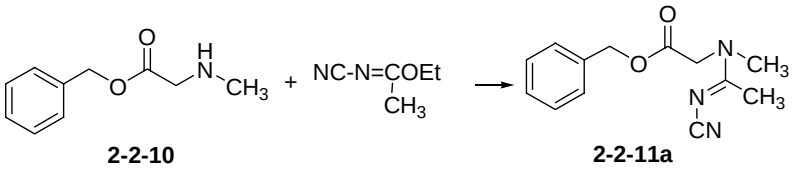


To effect the formation of **2-2-12**, we eventually replaced NaOEt/EtOH with KO^{t}Bu/^{t}BuOH which also provided a rapid imidazole ring formation but without displacement of the benzyl group. Due to the EtOH formation during the reaction from **2-2-10** to **2-2-11**, it was impossible to carry out these two steps in one pot as demonstrated in our solution-phase study (Scheme 2-4). Hence a two pot procedure was adopted.

2.2.2.1.3 Synthesis of benzyl 2-(*N*-butyl-*N'*-cyanoacetamidino)acetate (2-2-11a) and benzyl 2-(*N*-butyl-*N'*-cyanobenzamidino)acetate (2-2-11b)

To increase the diversity of substituents at the C8 position, benzyl *N*-methyl glycinate (**2-2-10a**), was treated with methyl ethoxymethylene cyanamide or phenyl ethoxymethylene cyanamide. Unlike the reaction of **2-2-10** with ethoxymethylene cyanamide, which occurred very rapidly in either EtOH, THF or DMF without any other reagents or catalysts, these reactions only proceeded in the presence of base (Schemes 2-9 and 2-10, Table 2-4). Various conditions were tested to improve the yield and it was found that DBU was a better base for this reaction than DIEA.

Scheme 2-9 Synthesis of **2-2-11a**

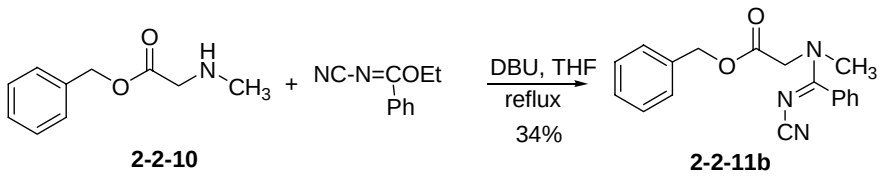


2-2-10 **2-2-11a**

Table 2-4 Synthesis of **2-2-11a**

Entry	*Base*	*Solvent*	*Conditions*	*Result*
1	None	THF	rt, 24 h	No reaction
2	None	THF	reflux, 24 h	Trace product
3	DIEA	THF	rt, 2.5 h	20% yield
4	DIEA	THF	rt, 24 h	48% yield
5	DBU	THF	rt, 2.5 h	62% yield

Scheme 2-10 Synthesis of **2-2-11b**



2-2-10 **2-2-11b**

2.2.2.1.4 Synthesis of benzyl 5-amino-3-butyl-3*H*-imidazole-4-carboxylate (2-2-12)

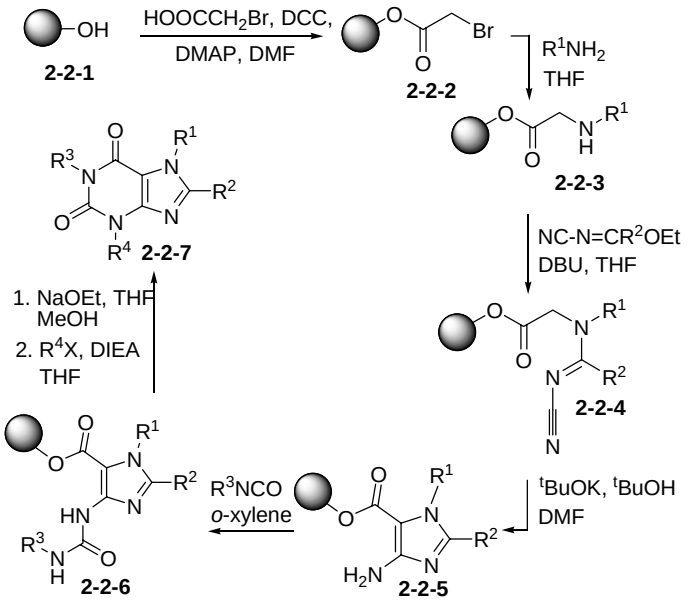
As ethoxide is able to attack the ester group of **2-2-11** easily, we reasoned that a bulky alkoxide must be used to avoid such a reaction from occurring. Hence $KO^tBu/^tBuOH$ was tried, and we found that the reaction was completed in 30 min to give **2-2-12** in moderate yield (52%).

2.2.2.1.5 Synthesis of benzyl 3-butyl-5-(3-hexylureido)-3*H*-imidazole-4-carboxylate (2-2-13) and 7-butyl-1-hexylxanthine (2-2-7a)

With **2-2-12** in hand, we proceeded to treat it with hexyl isocyanate which provided **2-2-13** in 90% yield. Subsequent ring closure of **2-2-13** with NaOEt in MeOH-THF mixture afforded **2-2-7a** in good yield.

2.2.2.2 Traceless solid-phase synthesis of substituted xanthines

Scheme 2-11 Traceless SPS of Substituted Xanthines

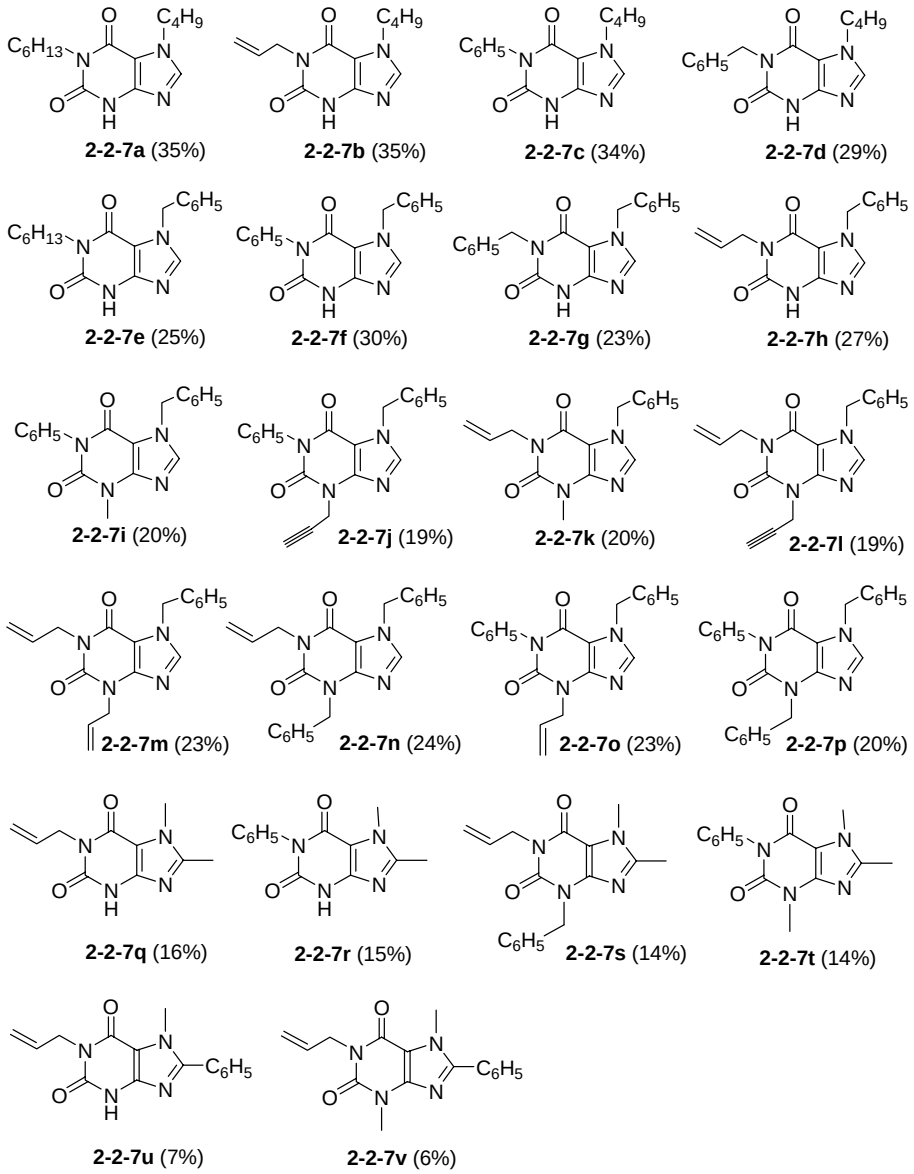


With the solution-phase pathway established, we proceeded to prove the applicability of this methodology in solid-phase synthesis (Scheme 2-11).

Wang resin **2-2-1** in DCC/DMAP/DMF was allowed to react with bromoacetic acid at rt. The formation of **2-2-2** was amenable to KBr FTIR monitoring (*i.e.* disappearance of the OH stretch at 3566 cm^{-1} and the appearance of a strong C=O stretch at 1744 cm^{-1}). Resin **2-2-2** was then treated with various primary amines in THF to give **2-2-3**, which was subsequently reacted with ethoxymethylene cyanamide, methyl ethoxymethylene cyanamide or phenyl ethoxymethylene cyanamide in the presence of DBU, to provide resin **2-2-4**. Due to the poor swelling ability of polystyrene/1% divinylbenzene in ^{t}BuOH, cyclization of **2-2-4** using KO^{t}Bu was carried out in a DMF/^{t}BuOH (v/v 1:1) mixture. The disappearance of the CN stretch at 2178 cm^{-1} and the shift of the C=O stretch from 1744 cm^{-1} to 1690 cm^{-1} were indicative of the formation of **2-2-5**. Treatment of **2-2-5** with various isocyanates in *o*-xylene (120-125 °C, 24 h) provided **2-2-6**, which underwent a concomitant cyclization-cleavage in

NaOEt in MeOH/THF (v/v 1:2) to give 1,7- or 1,7,8- substituted xanthines which was subsequently alkylated in an one-pot reaction to afford the fully-substituted xanthines. To illustrate the versatility of this chemistry, a representative set of 22 compounds (**2-2-7a - 2-2-7v**) was prepared (Figure 2-5). The overall yields obtained were 14-35% (purities of > 95% by NMR) for compounds **2-2-7a - 2-2-7t**, indicating an average yield of ≥ 75% for each step of the solid-phase reaction. However for compounds **2-2-7u** and **2-2-7v**, where the C8 substituent is a phenyl group, lower yields were obtained.

Figure 2-5 Library of Substituted Xanthines **2-2-7**



2.3 Conclusion

These studies investigated the methodologies for the solid-phase synthesis of xanthines. Two solution-phase synthetic routes were successfully carried out to obtain the required reaction conditions which would be adaptable to solid-phase reactions. Eventually two solid-phase synthetic routes to xanthines were developed.

2.4 Experimental

Wang resin was purchased from Tianjin Nankai Hecheng Science and Technology Co (100-200 mesh, 1.4 mmol/g, 1% divinylbenzene cross-linking). All other chemical reagents were obtained from Aldrich, Merck, Lancaster or Fluka and used without further purification. The solid-phase rt reactions were agitated on a SF1 flask shaker (Stuart Scientific). Analytical TLC was carried out on pre-coated plates (Merck silica gel 60, F254) and visualized with UV light or stained with ninhydrin. CC was performed with silica (Merck, 70-230 mesh). ^{1}H NMR and ^{13}C NMR spectra were measured at 298 K on a Bruker DPX 300 or DPX 500 Fourier Transform spectrometer. Chemical shifts are reported in δ (ppm), relative to the internal standard of TMS. The signals observed are described as: s, d, t, q, m. The number of protons (n) for a given resonance is indicated as nH. All Infra-red spectra were recorded on a Bio-Rad FTS 165 spectrometer. Mass spectra were performed on VG Micromass 7035 spectrometer under EI, Finnigan/MAT LCQ under ESI (Normal), and Finnigan/MAT 95XL-T under ESI (Accurate).

2.4.1 Solid-phase synthesis of 1,3-substituted xanthines

2.4.1.1 Synthesis of ethyl *N*-(2,4-dimethoxybenzyl) glycinate (2-1-8)

To 2,4-dimethoxylbenzaldehyde (0.1660 g, 1 mmol) in DMF (5 mL) was added ethyl

glycinate hydrochloride (0.2790 g, 2 mmol) and triethylamine (0.2780 mL, 2 mmol). The mixture was stirred for 5 min and sodium triacetoxyborohydride (0.4240 g, 2 mmol) and HOAc (0.1 mL) were added. After that, the reaction mixture was stirred at rt for another 8 h. The reaction was quenched with saturated $NaHCO_3$ and concentrated. The residue obtained was diluted with water (50 mL), and extracted with EtOAc (50 mL x 3). The combined organic layer was dried with $MgSO_4$, filtered, concentrated and purified by CC (EtOAc:hexane = 4:1, then MeOH:CH_2Cl_2 = 1:7) to give **2-1-8** as a colorless liquid (0.2400 g, 95% yield). ^{1}H NMR ($CDCl_3$): δ 7.12-7.09 (d, *J* = 7.7 Hz, *ArH*, 1H), 6.44-6.39 (m, *ArH*, 2H), 4.18-4.10 (q, *J* = 7.1 Hz, CH_3CH_2, 2H), 3.80 (s, ArOCH_3, 3H), 3.78 (s, ArOCH_3, 3H), 3.73 (s, ArCH_2, 2H), 3.35 (s, NHCH_2CO, 2H), 2.10 (s, *NH*, 1H), 1.27-1.22 (t, *J* = 7.1 Hz, CH_3CH_2, 3H); ^{13}C NMR ($CDCl_3$): δ 172.2, 160.0, 158.4, 130.3, 119.8, 103.5, 98.2, 60.3, 55.0, 49.8, 47.8, 13.9; Mass spectrum (EI) m/z 253.2 (M^+) Exact mass calcd for $C_{13}H_{19}NO_4$: m/z 253.1314; found 253.1304.

2.4.1.2 Synthesis of ethyl 5-amino-3-(2,4-dimethoxybenzyl)-3*H*-imidazole-4-carboxylate (2-1-10)

Compound **2-1-8** (0.1226 g, 0.484 mmol) was dissolved in EtOH (5 mL) and the solution was cooled in a dry ice-acetone bath. Ethoxymethylene cyanamide (0.0520 g, 0.532 mmol) in EtOH (5 mL) was added dropwise, after which the dry ice-acetone bath was removed and the reaction mixture was stirred at rt for 2 h. The reaction mixture was subsequently cooled in a dry ice-acetone bath and NaOEt (21% (w/w) in denatured EtOH, 0.18 mL, 0.484 mmol) was then added. The reaction mixture was stirred at rt for another 20 h. After which, the mixture was concentrated and purified by CC (EtOAc:CH_2Cl_2 = 2:1) to give **2-1-10** as a colorless solid

(0.1030 g, 70% yield). ^{1}H NMR ($CDCl_3$): δ 7.18 (s, *CH*, 1H), 7.09-7.06 (d, *J* = 8.0 Hz, *ArH*, 1H), 6.45-6.40 (m, *ArH*, 2H), 5.25 (s, ArCH_2, 2H), 4.83 (s, NH_2, 2H), 4.32-4.25 (q, *J* = 7.2 Hz, CH_3CH_2, 2H), 3.81 (s, ArOCH_3, 3H), 3.79 (s, ArOCH_3, 3H), 1.34-1.29 (t, *J* = 7.1 Hz, CH_3CH_2, 3H); ^{13}C NMR ($CDCl_3$): δ 161.1, 161.0, 158.2, 155.4, 139.5, 130.3, 117.1, 104.2, 102.0, 98.4, 59.5, 55.3, 55.3, 45.5, 14.4; Mass spectrum (EI) m/z 305.0 (M^+) Exact mass calcd for $C_{15}H_{19}N_3O_4$: m/z 305.1376; found 305.1377.

2.4.1.3 Synthesis of ethyl 3-(2,4-dimethoxybenzyl)-5-(3-phenylureido)-3*H*-imidazole-4-carboxylate (2-1-11)

To **2-1-10** (0.1000 g, 0.328 mmol) was added *o*-xylene (6 mL), and phenyl isocyanate (0.12 mL, 0.984 mmol) and the mixture was heated at 120 °C for 8 h. After which, the mixture was concentrated and purified by CC (EtOAc:hexane = 1:3) to give **2-1-11** as a colorless oil (0.1253 g, 90% yield). ^{1}H NMR ($CDCl_3$): δ 11.06 (s, Ar*NH*CO, 1H), 8.08 (s, *NH*, 1H), 7.58-7.55 (*CH* and *ArH*, 2H), 7.33-7.26 (m, *ArH*, 3H), 7.14-7.12 (d, *J* = 8.0 Hz, *ArH***,** 1H), 7.05-7.00 (t, *J* = 7.0 Hz, *ArH*, 1H), 6.46-6.42 (m, *ArH*, 2H), 5.32 (s, ArCH_2, 2H), 4.40-4.33 (q, *J* = 7.1 Hz, CH_3CH_2**,** 2H), 3.80 (s, ArOCH_3**,** 3H), 3.78 (s, ArOCH_3**,** 3H), 1.39-1.34 (t, *J* = 7.0 Hz, CH_3CH_2, 3H); ^{13}C NMR ($CDCl_3$): δ 161.3, 159.9, 158.3, 151.8, 147.2, 138.6, 137.7, 130.8, 128.7, 122.9, 119.7, 115.7, 104.3, 103.8, 98.5, 60.5, 55.2, 45.9, 14.3; Mass spectrum (EI) m/z 424.0 (M^+) Exact mass calcd for $C_{22}H_{24}N_4O_5$: m/z 424.1747; found 424.1739.

2.4.1.4 Synthesis of 7-(2,4-dimethoxybenzyl)-1-phenylxanthine (2-1-12)

To **2-1-11** (0.1920 g, 0.450 mmol) in MeOH (6 mL) was added NaOEt (21% (w/w) in denatured EtOH, 0.5 mL, 1.360 mmol). The mixture was refluxed for 2 h, after which the mixture was concentrated and the resulting residue was diluted with water (10 mL) and

acidified with 1.5 M HCl. The white precipitate which formed was filtered, washed with water and dried to give **2-1-12** as a white power (0.1702 g, 100% yield). ^{1}H NMR (DMSO-d_6): δ 11.96 (s, *NH*, 1H), 7.95 (s, *CH*, 1H), 7.48-7.36 (m, *ArH*, 3H), 7.24-7.22 (d, *J* = 7.0 Hz, ***ArH,*** 2H), 7.14-7.12 (d, *J* = 8.3 Hz, *ArH*, 1H), 6.57-6.45 (m, *ArH*, 2H), 5.28 (s, Ar*CH*$_2$, 2H), 3.81 (s, ArO*CH*$_3$**,** 3H), 3.73 (s, ArO*CH*$_3$**,** 3H); ^{13}C NMR (DMSO-d_6): δ 160.7, 158.1, 155.0, 150.9, 148.0, 143.1, 135.8, 130.3, 129.3, 128.6, 127.8, 116.4, 106.1, 104.6, 98.4, 55.4, 55.2, 44.3, 40.3; Mass spectrum (EI) m/z 378.2 (M^+) Exact mass calcd for $C_{20}H_{18}N_4O_4$: m/z 378.1328; found 378.1339.

2.4.1.5 Synthesis of 7-(2,4-dimethoxybenzyl)-3-methyl-1-phenylxanthine (2-1-13)

To a mixture of **2-1-12** (0.0200 g, 0.0529 mmol) in DMF (3 mL) and DIEA (0.19 mL, 1.060 mmol) was added MeI (0.033 mL, 0.529 mmol) dropwise. The reaction mixture was stirred for 1 h at rt and then concentrated. The resulting residue was purified by CC (MeOH:CH_2Cl_2 = 1:7) to give **2-1-13** as a white solid (0.0199 g, 96% yield). ^{1}H NMR ($CDCl_3$): δ 7.71 (s, *CH*, 1H), 7.54-7.41 (m, *ArH*, 4H), 7.27-7.24 (m, *ArH,* 2H), 6.45-6.41 (m, *ArH,* 2H), 5.40 (s, Ar*CH*$_2$, 2H), 3.85 (s, ArO*CH*$_3$**,** 3H), 3.79 (s, ArO*CH*$_3$**,** 3H), 3.58 (s, *CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 161.7, 158.6, 155.2, 151.7, 149.3, 142.1, 135.7, 132.3, 129.3, 128.8, 128.6, 116.0, 107.1, 104.4, 98.6, 55.4, 45.2, 29.7; Mass spectrum (EI) m/z 392.0 (M^+) Exact mass calcd for $C_{21}H_{20}N_4O_4$: m/z 392.1485; found 392.1482.

2.4.1.6 Synthesis of 3-methyl-1-phenylxanthine (2-1-7b)

A mixture of **2-1-13** (0.1000 g, 0.255 mmol), TFA (9 mL) and CH_2Cl_2 (1 mL) was refluxed for 1 h. The mixture was concentrated and purified by CC (MeOH:CH_2Cl_2 = 1:10) to give **2-1-7b** as a white solid (0.0555 g, 90% yield). ^{1}H NMR ($CDCl_3$): δ 12.41 (s, *N7H*, 1H), 7.52-

7.42 (m, *ArH* and *CH*, 4H), 7.26-7.24 (d, *J* = 7.3 Hz, *ArH*, 2H), 3.64 (s, CH_3, 3H); ^{13}C NMR ($CDCl_3$): δ 155.8, 151.6, 149.4, 140.6, 135.5, 129.4, 128.8, 128.7, 107.1, 30.3; Mass spectrum (EI) m/z 242.1 (M^+) Exact mass calcd for $C_{12}H_{10}N_4O_2$: m/z 242.0804; found 242.0802.

2.4.1.7 Preparation of ethyl *N*-(2-methoxy-4-phenoxybenzyl) glycinate resin (2-1-2)

PS-MB-CHO resin **2-1-1** (3.000 g, 4.02 mmol) was placed in a dry 100 mL round bottom flask, ethyl glycinate hydrochlodride (1.6830 g, 12.06 mmol), DMF (30 mL) and TEA (1.68 mL, 12.06 mmol) were added and the mixture was shaken at rt for 30 min. After which, sodium triacetoxyborohydride (2.5560 g, 12.06 mmol) and HOAc (0.3 mL) were added and the reaction mixture was shaken at rt for another 24 h. The reaction was quenched with saturated $NaHCO_3$, filtered and washed with DMF (20 mL x 3), H_2O (20 mL x 3), EtOH (20 mL x 3), CH_2Cl_2 (20 mL x 3) and Et_2O (20 mL x 3). The resin was then dried overnight at 50 °C in a vacuum oven.

2.4.1.8 Preparation of ethyl 4-amino-1-(2-methoxy-4-phenoxybenzyl)-imidazole-5-carboxylate resin (2-1-3)

To a stirring suspension of **2-1-2** (3.325 g, 4.02 mmol) in DMF (52.8 mL) and EtOH (80 mL) was cooled in a dry ice-actone bath. A solution of ethoxymethylene cyanamide (0.7880 g, 8.04 mmol) in anhydrous EtOH (25 mL) was added dropwise and the mixture was shaken at rt for 24 h. After which, the reaction mixture was cooled in a dry ice-acetone bath again and NaOEt (21% (w/w) in denatured EtOH, 3 mL, 8.04 mmol) was added dropwise. The mixture was shaken at rt for another 24 h. The resin was filtered, washed with DMF (20 mL x 3), H_2O (20 mL x 3), EtOH (20 mL x 3), CH_2Cl_2 (20 mL x 3), Et_2O (20 mL x 3) and dried overnight at 50 °C in a vacuum oven.

2.4.1.9 Preparation of ethyl 4-(3-substitutedureido)-1-(2-methoxy-4-phenoxybenzyl)-imidazole-5-carboxylate resin (2-1-4)

Resin **2-1-3** (0.3000 g, 0.3386 mmol), isocyanates (5 equiv), and *o*-xylene (6 mL) were heated at 120 °C for 24 h. The resin was then filtered, washed with EtOH (20 mL x 3), CH_2Cl_2 (20 mL x 3), Et_2O (20 mL x 3) and dried overnight at 50 °C in vacuum oven.

2.4.1.10 Preparation of 1-substituted-7-(2-methoxy-4-phenoxybenzyl)xanthine resin (2-1-5)

A mixture of resin **2-1-4** (0.3300 g, 0.3386 mmol), NaOEt (21% (w/w) in denatured EtOH, 0.8 mL, 5 equiv), anhydrous THF (5 mL) and anhydrous MeOH (15 mL) was refluxed for 12 h. The resin was then filtered, acidified with 1.5 M HCl, washed with H_2O (20 mL x 3), EtOH (20 mL x 3), CH_2Cl_2 (20 mL x 3) and dried overnight at 50 °C in a vacuum oven.

2.4.1.11 Preparation of 1,3-substituted-7-(2-methoxy-4-phenoxybenzyl)xanthine resin (2-1-6)

Resin **2-1-5** (0.3300 g, 0.3386 mmol) was swelled in DMF (6 mL). DIEA (1.2 mL, 20 equiv) and the respective halide (10 equiv) were added and the mixture was shaken at rt for 24 h. After which, the resin was filtered, washed with DMF (20 mL x 3), H_2O (20 mL x 3), EtOH (20 mL x 3), CH_2Cl_2 (20 mL x 3), Et_2O (20 mL x 3) and dried overnight at 50 °C in vacuum oven.

2.4.1.12 Preparation of 1,3-substituted xanthine (2-1-7a - 2-1-7l)

A mixture of resin **2-1-6** (0.3400 g, 0.3386 mmol), TFA (9 mL) and CH_2Cl_2 (1 mL) was shaken at rt for 12 h. The resin was then filtered and washed with MeOH (20 mL x 3) and

CH_2Cl_2 (20 mL x 3). The combined filtrate was concentrated and the residue was purified by CC (EtOAc:CH_2Cl_2 = 1.5:1) to give xanthine **2-1-7**.

2.4.1.13 Preparation of 1-substituted thioxanthine (2-1-7m - 2-1-7p)

A mixture of resin **2-1-6** (0.3600 g, 0.3386 mmol), TFA (9 mL) and CH_2Cl_2 (1 mL) was shaken at rt for 12 h. After which, the resin was filtered and washed with MeOH (20 mL x 3) and CH_2Cl_2 (20 mL x 3). The resulting resin was then refluxed with HOAc (8 mL, 140 mmol) for 24 h. After which, the resin was filtered and washed with MeOH (20 mL x 3) and CH_2Cl_2 (20 mL x 3). The combined filtrate was concentrated to dryness and the solid obtained was washed with cold EtOAc to give thioxanthine **2-1-7**.

2-1-7a: 1-Phenylxanthine. ^{1}H NMR (DMSO-d_6): δ 13.48 (s, *N3H*, 1H), 11.95 (s, *N7H*, 1H), 8.01 (s, *CH*, 1H), 7.48-7.37 (m, *ArH*, 3H), 7.27-7.24 (d, *J* = 7.3 Hz, *ArH*, 2H); ^{13}C NMR (DMSO-d_6): δ 155.1, 151.1, 147.7, 140.9, 136.2, 129.3, 128.7, 127.8, 106.5; Mass spectrum (EI) m/z 228.2 (M^+) Exact mass calcd for $C_{11}H_8N_4O_2$: m/z 228.0647; found 228.0644.

2-1-7c: 3-Benzyl-1-phenylxanthine. ^{1}H NMR ($CDCl_3$): δ 12.29 (s, *N7H*, 1H), 7.57-7.39 (m, *CH* and *ArH*, 6H), 7.33-7.22 (m, *ArH*, 5H), 5.31 (s, Ar*CH*$_2$, 2H); ^{13}C NMR ($CDCl_3$): δ 155.9, 151.3, 149.2, 140.5, 136.1, 135.4, 129.4, 129.0, 128.8, 128.7, 128.5, 128.0, 107.2, 47.2; Mass spectrum (EI) m/z 318.0 (M^+) Exact mass calcd for $C_{18}H_{14}N_4O_2$: m/z 318.1117; found 318.1111.

2-1-7d: 1-Phenyl-3-propargylxanthine. ^{1}H NMR (CD_3OD): δ 8.00 (s, *CH*, 1H), 7.53-7.42 (m, *ArH*, 3H), 7.29-7.26 (d, *J* = 7.0 Hz, *ArH*, 2H), 4.89-4.88 (d, *J* = 2.4 Hz, N3*CH*$_2$, 2H), 2.71-2.69 (t, *J* = 2.3 Hz, CH_2C*CH*, 1H); ^{13}C NMR (CD_3OD): δ 156.3, 152.6, 149.0, 142.0, 137.1, 130.3, 130.1, 129.7, 108.9, 78.6, 73.3, 33.9; Mass spectrum (EI) m/z 266.0 (M^+) Exact

mass calcd for $C_{14}H_{10}N_4O_2$: m/z 266.0804; found 266.0805.

2-1-7e: 1-Allylxanthine. ^{1}H NMR (CD_3OD): δ 7.88 (s, *CH*, 1H), 5.98-5.85 (m, CH_2*CH*CH_2, 1H), 5.20-5.11 (m, CH_2CH*CH*$_2$, 2H), 4.58-4.55 (m, N1*CH*$_2$, 2H); ^{13}C NMR (CD_3OD): δ 156.97, 153.2, 148.4, 141.7, 133.7, 117.2, 108.6, 43.6; Mass spectrum (EI) m/z 192.0 (M^+) Exact mass calcd for $C_8H_8N_4O_2$: m/z 192.0647; found 192.0648.

2-1-7f: 1-Allyl-3-methylxanthine. ^{1}H NMR ($CDCl_3$): δ 13.02 (s, *NH*, 1H), 7.82 (s, *CH*, 1H), 6.00-5.87 (m, CH_2*CH*CH_2, 1H), 5.29-5.18 (m, CH_2CH*CH*$_2$**,** 2H), 4.71-4.69 (d, *J* = 5.6 Hz, N1*CH*$_2$**,** 2H), 3.65 (s, *CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 155.9, 151.0, 149.2, 140.4, 132.0, 117.7, 106.9, 43.8, 30.2; Mass spectrum (EI) m/z 206.2 (M^+) Exact mass calcd for $C_9H_{10}N_4O_2$: m/z 206.0804; found 206.0808.

2-1-7g: 1-Allyl-3-benzylxanthine. ^{1}H NMR ($CDCl_3$): δ 7.93 (s, *CH*, 1H), 7.40-7.24 (m, *ArH*, 5H), 5.97-5.84 (m, CH_2*CH*CH_2, 1H), 5.29 (s, Ar*CH*$_2$, 2H), 5.17~5.11 (m, *CH*$_2$, 2H), 4.61-4.59 (d, *J* = 5.2 Hz, N1*CH*$_2$, 2H); ^{13}C NMR ($CDCl_3$): δ 155.7, 150.9, 148.8, 140.1, 136.3, 132.1, 128.7, 128.6, 127.9, 117.9, 107.0, 47.1, 43.8; Mass spectrum (EI) m/z 282.2 (M^+) Exact mass calcd for $C_{15}H_{14}N_4O_2$: m/z 282.1117; found 282.1118.

2-1-7h: 1-Allyl-3-propargylxanthine. ^{1}H NMR ($CDCl_3$): δ 12.75 (s, *NH*, 1H), 7.87 (s, *CH*, 1H), 6.01-5.88 (m, CH_2*CH*CH_2, 1H), 5.32-5.20 (m, CH_2CH*CH*$_2$, 2H), 4.95-4.95 (d, *J* = 2.5 Hz, N3*CH*$_2$, 2H), 4.72-4.70 (d, *J* = 5.9 Hz, N1*CH*$_2$, 2H), 2.29-2.27 (t, *J* = 2.5 Hz, CH_2C*CH*, 1H); ^{13}C NMR ($CDCl_3$): δ 155.7, 150.2, 147.9, 140.5, 131.8, 118.0, 116.2, 107.1, 72.1, 43.9, 33.0; Mass spectrum (EI) m/z 230.0 (M^+) Exact mass calcd for $C_{11}H_{10}N_4O_2$: m/z 230.0804; found 230.0802.

2-1-7i: 1-Benzylxanthine. ^{1}H NMR (DMSO-d_6): δ 13.43 (s, *N3H*, 1H), 11.93 (s, *N7H*, 1H),

7.99 (s, *CH*, 1H), 7.29-7.22 (m, *ArH*, 5H), 5.03 (s, Ar*CH*$_2$, 2H); ^{13}C NMR (DMSO-d$_6$): δ 154.9, 151.0, 147.3, 141.0, 137.8, 128.2, 127.2, 126.8, 106.1, 42.9; Mass spectrum (EI) m/z 242.0 (M^+) Exact mass calcd for $C_{12}H_{10}N_4O_2$: m/z 242.0804; found 242.0795.

2-1-7j: 1-Benzyl-3-methylxanthine. ^{1}H NMR ($CDCl_3$): δ 7.70 (s, *CH*, 1H), 7.47-7.45 (d, *J* = 6.6 Hz, *ArH*, 2H), 7.32-7.25 (m, *ArH*, 3H), 5.27 (s, Ar*CH*$_2$, 2H), 3.64 (s, *CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 156.1, 151.3, 149.1, 140.4, 137.0, 128.5, 128.4, 127.6, 106.9, 45.0, 30.3; Mass spectrum (EI) m/z 256.1 (M^+) Exact mass calcd for $C_{13}H_{12}N_4O_2$: m/z 256.0960; found 256.0961.

2-1-7k: 1,3-Dibenzylxanthine. ^{1}H NMR ($CDCl_3$): δ 12.78 (s, *NH*, 1H), 7.65 (s, *CH*, 1H), 7.49-7.43 (m, *ArH*, 4H), 7.31-7.25 (m, *ArH*, 6 H), 5.32 (s, N1*CH*$_2$, 2H), 5.27 (s, N3*CH*$_2$, 2H); ^{13}C NMR ($CDCl_3$): δ 156.2, 151.2, 148.9, 140.4, 137.0, 136.2, 128.5, 128.5, 128.4, 127.9, 127.6, 107.0, 47.1, 45.1; Mass spectrum (EI) m/z 332.0 (M^+) Exact mass calcd for $C_{19}H_{16}N_4O_2$: m/z 332.1273; found 332.1276.

2-1-7l: 1-Benzyl-3-propargylxanthine. ^{1}H NMR ($CDCl_3$): δ 12.71 (s, *NH*, 1H), δ 7.75 (s, *CH*, 1H), δ 7.48-7.46 (d, *J* = 6.6 Hz, *ArH*, 2H), δ 7.34-7.24 (m, *ArH*, 3H), δ 5.28 (s, Ar*CH*$_2$, 2H), δ 4.94-4.93 (d, *J* = 2.4 Hz, N3*CH*$_2$, 2H), δ 2.28-2.27 (t, *J* = 2.4 Hz, CH$_2$C*CH*, 1H); ^{13}C NMR ($CDCl_3$): δ 156.1, 150.6, 148.0, 140.5, 136.8, 128.7, 128.5, 127.8, 107.1, 77.4, 72.1, 45.2, 33.1; Mass spectrum (EI) m/z 280.1 (M^+) Exact mass calcd for $C_{15}H_{12}N_4O_2$: m/z 280.0960; found 280.0958.

2-1-7m: 1-Propyl-2-thioxanthine. ^{1}H NMR (DMSO-d$_6$): δ 13.65 (s, *N3H*, 1H), 13.49 (s, *N7H*, 1H), 8.09 (s, *CH*, 1H), 4.36-4.31 (t, *J* = 7.7 Hz, N1*CH*$_2$, 2H), 1.71-1.63 (m, CH$_3$*CH*$_2$CH$_2$, 2H), 0.91-0.87 (t, *J* = 7.3 Hz, *CH*$_3$, 3H); ^{13}C NMR (DMSO-d$_6$): δ 173.9, 153.4,

147.2, 142.0, 109.8, 47.1, 19.7, 11.1; Mass spectrum (EI) m/z 210.0 (M^+) Exact mass calcd for $C_8H_{10}N_4OS$: m/z 210.0575; found 210.0570.

2-1-7n: 1-Ethyl-2-thioxanthine. ^{1}H NMR (DMSO-d_6): δ 13.67 (s, *N3H*, 1H), 13.51 (s, *N7H*, 1H), 8.11 (s, *CH*, 1H), 4.48-4.42 (q, *J* = 6.9 Hz, CH_3CH_2, 2H), 1.22-1.18 (t, *J* = 6.9 Hz, CH_3CH_2, 3H); ^{13}C NMR (DMSO-d_6): δ 173.6, 153.1, 147.2, 142.0, 109.0, 41.0, 12.0; Mass spectrum (EI) m/z 196.0 (M^+) Exact mass calcd for $C_7H_8N_4OS$: m/z 196.0419; found 196.0412.

2-1-7o: 1-Benzyl-2-thioxanthine. ^{1}H NMR (DMSO-d_6): δ 13.66 (s, *N3H*, 2H), 8.14 (s, *CH*, 1H), 7.31-7.21 (m, *ArH*, 5H), 5.66 (s, ArCH_2, 2H); ^{13}C NMR (DMSO-d_6): δ 174.5, 153.4, 147.3, 142.2, 136.8, 128.1, 126.9, 126.7, 109.9, 48.6; Mass spectrum (EI) m/z 258.2 (M^+) Exact mass calcd for $C_{12}H_{10}N_4OS$: m/z 258.0575; found 258.0576.

2-1-7p: 1-Phenyl-2-thioxanthine. ^{1}H NMR (DMSO-d_6): δ 14.15 (s, *N3H*, 1H), 8.66 (s, *CH*, 1H), 8.00-7.89 (m, *ArH*, 3H), 7.73-7.71 (d, *J* = 7.3 Hz, *ArH*, 2H); ^{13}C NMR (DMSO-d_6): δ 174.8, 153.3, 147.2, 141.4, 139.2, 128.7, 128.3, 127.3, 110.3; Mass spectrum (EI) m/z 244.1 (M^+) Exact mass calcd for $C_{11}H_8N_4OS$: m/z 244.0419; found 244.0409.

2.4.2 Traceless solid-phase synthesis of substituted xanthines

2.4.2.1 Synthesis of benzyl bromoacetate (2-2-9)

To benzyl alcohol **2-2-8** (0.2000 g, 1.849 mmol) in DMF (5 mL) was add bromoacetic acid (0.5131 g, 3.698 mmol), DCC (0.7630 g, 3.698 mmol) and DMAP (0.0677 g, 0.5547 mmol) in the stated order. The reaction mixture was stirred at rt for 2 h, then quenched with water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layer was dried with $MgSO_4$, filtered, concentrated and purified by CC (EtOAc:hexane = 1:20) to give **2-2-9** as a

pale yellow liquid (0.4201 g, 99% yield). ^{1}H NMR ($CDCl_3$): δ 7.41-736 (m, *ArH*, 5H), 5.21 (s, Ar*CH*$_2$, 2H), 3.87 (s, *CH*$_2$Br, 2H); ^{13}C NMR ($CDCl_3$): δ 166.8, 134.8, 128.4, 128.4, 128.2, 67.7, 25.7; Mass spectrum (EI) m/z 227.8 (M^+) Exact mass calcd for $C_9H_9BrO_2$: m/z 227.9786; found 227.9790.

2.4.2.2 Synthesis of benzyl *N*-butyl glycinate (2-2-10)

Compound **2-2-9** (0.5031 g, 2.20 mmol) was dissolved in THF (25 mL) and the solution was cooled in an ice-water bath. Butylamine (0.3213 g, 4.40 mmol) was diluted in THF (25 mL) and the solution was added to **2-2-9** dropwise. After which, the ice-water bath was removed and the reaction mixture was stirred at rt for 2 h. This mixture was concentrated and purified by CC (EtOAc:hexane = 1:3 then MeOH:CH_2Cl_2 = 1:20) to give **2-2-10** as a colorless liquid (0.3702 g, 76% yield). ^{1}H NMR ($CDCl_3$): δ 7.35 (s, *ArH*, 5H), 5.16 (s, Ar*CH*$_2$, 2H), 3.45 (s, CO*CH*$_2$NH, 2H), 2.62-2.57 (t, *J* = 6.96 Hz, NH*CH*$_2$CH$_2$CH$_2$CH$_3$**,** 2H), 1.99 (s, *NH*, 1H), 1.52-1.42 (m, NHCH$_2$*CH*$_2$CH$_2$CH$_3$, 2H), 1.40-1.28 (m, NHCH$_2$CH$_2$*CH*$_2$CH$_3$, 2H), 0.93-0.88 (t, *J* = 7.14 Hz, NHCH$_2$CH$_2$CH$_2$*CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 172.3, 135.5, 128.4, 128.2, 128.2, 66.3, 50.8, 49.1, 32.0, 20.2, 13.8; Mass spectrum (EI) m/z 221.1 (M^+) Exact mass calcd for $C_{13}H_{19}NO_2$: m/z 221.1416; found 221.1408.

2.4.2.3 Synthesis of benzyl 2-(*N*-butyl-*N'*-cyanoformamidino)acetate (2-2-11)

Compound **2-2-10** (0.1362 g, 0.6155 mmol) in THF (3 mL) was cooled in an ice-water bath and ethoxymethylene cyanamide (0.1207 g, 1.231 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred at rt for 2 h. The mixture was concentrated and purified by CC (EtOAc:hexane = 1:1) to obtain **2-2-11** as a colorless liquid (0.1649 g, 98% yield). ^{1}H NMR ($CDCl_3$): δ 8.13 (s, CH, 1H), 7.37-7.32 (m, *ArH*, 5H), 5.17 (s, Ar*CH*$_2$, 2H), 4.14 (s,

CO*CH*$_2$N, 2H), 3.39-3.34 (t, *J* = 7.31 Hz, N*CH*$_2$CH$_2$CH$_2$CH$_3$**,** 2H), 1.60-1.50 (m, NCH$_2$*CH*$_2$CH$_2$CH$_3$, 2H), 1.36-1.24 (m, NCH$_2$CH$_2$*CH*$_2$CH$_3$, 2H), 0.93-0.89 (t, *J* = 7.40 Hz, CH$_2$CH$_2$CH$_2$*CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 166.6, 163.9, 134.6, 128.3, 128.2, 127.9, 117.5, 67.1, 52.8, 46.7, 29.6, 19.1, 13.2; Mass spectrum (EI) m/z 273.0 (M^+) Exact mass calcd for $C_{15}H_{19}N_3O_2$: m/z 273.1477; found 273.1475.

2.4.2.4 Synthesis of benzyl 5-amino-3-butyl-3*H*-imidazole-4-carboxylate (2-2-12)

To **2-2-11** (0.1500 g, 0.5488 mmol) in THF (5 mL) was added ^{t}BuOH (5 mL) and KO^{t}Bu (0.0616 g, 1.0976 mmol) and the reaction mixture was stirred for 1 h. After which, the reaction mixture was quenched with NH_4Cl, diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (30 mL x 3). The combined organic layer was dried with $MgSO_4$, filtered, concentrated and purified by CC (EtOAc:CH_2Cl_2 = 2:1) to give a colorless solid **2-2-12** (0.0757 g, 52% yield). ^{1}H NMR ($CDCl_3$): δ 7.33-7.21 (m, *ArH*, 5H), 7.09 (s, *CH*, 1H), 5.20 (s, Ar*CH*$_2$, 2H), 4.70 (s, *NH*$_2$, 2H), 4.00-3.95 (t, *J* = 7.13 Hz, N*CH*$_2$CH$_2$CH$_2$CH$_3$, 2H), 1.63-1.53 (m, NCH$_2$*CH*$_2$CH$_2$CH$_3$, 2H), 1.20-1.08 (m, NCH$_2$CH$_2$*CH*$_2$CH$_3$, 2H), 0.80-0.76 (t, *J* = 7.31 Hz, NCH$_2$CH$_2$CH$_2$*CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 160.5, 155.8, 138.8, 136.0, 128.5, 128.1, 128.1, 101.1, 65.4, 47.2, 32.7, 19.4, 13.4; Mass spectrum (EI) m/z 273.1 (M^+) Exact mass calcd for $C_{15}H_{19}N_3O_2$: m/z 273.1477; found 273.1473.

2.4.2.5 Synthesis of benzyl 3-butyl-5-(3-hexylureido)-3*H*-imidazole-4-carboxylate (2-2-13)

To a solution of **2-2-12** (0.0814 g, 0.298 mmol) in *o*-xylene (7 mL) was added hexyl isocyanate (0.1895 g, 1.49 mmol) and the reaction mixture was heated at 120 °C for 8 h. After which, the resulting mixture was concentrated and purified by CC (EtOAc:hexane = 1:3 then EtOAc:hexane = 1:1) to give **2-2-13** (0.1133 g, 90% yield) as a white solid. ^{1}H NMR ($CDCl_3$):

δ 8.66 (s, C_6H_{13}*NH*CONH, 1H), 8.04 (s, C_6H_{13}NHCO*NH*, 1H), 7.43-7.28 (m, *CH* and *ArH*, 6H), 5.34 (s, Ar*CH*$_2$, 2H), 4.17-4.12 (t, *J* = 7.14 Hz, N*CH*$_2$CH$_2$CH$_2$CH$_3$, 2H), 3.35-3.28 (q, *J* = 6.50 Hz, NH*CH*$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$**,** 2H), 1.73-1.52 (m, NHCH$_2$*CH*$_2$CH$_2$CH$_2$CH$_2$CH$_3$ and NCH$_2$*CH*$_2$CH$_2$CH$_3$, 4H), 1.31-1.17 (m, NHCH$_2$CH$_2$*CH*$_2$*CH*$_2$*CH*$_2$CH$_3$ and NCH$_2$CH$_2$*CH*$_2$CH$_3$, 8H), 0.90-0.85 (m, NHCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$*CH*$_3$ and NCH$_2$CH$_2$CH$_2$*CH*$_3$, 6H); ^{13}C NMR ($CDCl_3$): δ 159.7, 154.6, 148.5, 137.2, 135.4, 128.8, 128.6, 128.5, 103.1, 66.3, 47.8, 40.1, 32.9, 31.5, 29.9, 26.7, 22.5, 19.6, 14.0, 13.5; Mass spectrum (EI) m/z 400.1 (M^+) Exact mass calcd for $C_{22}H_{32}N_4O_3$: m/z 400.2474; found 400.2471.

2.4.2.6 Synthesis of 7-butyl-1-hexylxanthine (2-2-7a)

THF (6 mL), MeOH (3 mL), followed by NaOEt (21% (w/w) in denatured EtOH, 0.32 mL, 0.849 mmol) were added to **2-2-13** (0.1133 g, 0.283 mmol). The mixture was refluxed at 90 °C for 1h. Subsequently, the mixture was concentrated and water (10 mL) was added. The precipitate that formed was removed after filtration. To the filtrate was added 1.5 M HCl acid dropwise till the pH < 6 and the precipitate that formed was collected and washed with cold water to give **2-2-7a** as a white solid (0.0744 g, 90% yield). ^{1}H NMR (Acetone-d_6): δ 10.83 (s, *NH*, 1H), 7.87 (s, *CH*, 1H), 4.35-4.30 (t, *J* = 7.07 Hz, N*CH*$_2$CH$_2$CH$_2$CH$_2$CH$_3$**,** 2H), 3.94-3.89 (t, *J* = 7.47 Hz, N*CH*$_2$CH$_2$CH$_2$CH$_3$**,** 2H), 1.89-1.80 (m, NCH$_2$*CH*$_2$CH$_2$CH$_2$CH$_2$CH$_3$, 2H), 1.63-1.58 (m, NCH$_2$*CH*$_2$CH$_2$CH$_3$, 2H), 1.43-1.29 (m, NCH$_2$CH$_2$*CH*$_2$*CH*$_2$*CH*$_2$CH$_3$ and NCH$_2$CH$_2$*CH*$_2$CH$_3$, 8H), 0.95-0.86 (m, CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$*CH*$_3$ and CH$_2$CH$_2$CH$_2$*CH*$_3$, 6H); ^{13}C NMR ($CDCl_3$): δ 156.8, 152.5, 149.3, 143.6, 108.0, 47.7, 41.5, 34.3, 32.9, 29.4, 28.0, 23.9, 20.8, 14.9, 14.5; Mass spectrum (EI) m/z 292.2 (M^+) Exact mass calcd for $C_{15}H_{24}N_4O_2$: m/z 292.1899; found 292.1901.

2.4.2.7 Preparation of benzyl bromoacetate resin (2-2-2)

Wang resin **(2-2-1)** (2 g, 2.8 mmol) was swollen in DMF (15 mL) for 30 min. Bromoacetic acid (0.7781 g, 5.6 mmol), DCC (1.1554 g, 5.6 mmol), DMAP (0.103 g, 0.84 mmol) were added in the stated order. The reaction mixture was shaken at rt for 5 h. After which, the resin was filtered, washed with DMF (20 mL x 3), H_2O (20 mL x 3), EtOH (20 mL x 3), CH_2Cl_2 (20 mL x 3), Et_2O (20 mL x 3) and dried overnight at 50 °C in a vacuum oven.

2.4.2.8 Preparation of benzyl *N*-substituted glycinate resin (2-2-3)

Resin **2-2-2** (2.8516 g, 2.8 mmol) was swollen in THF (30 mL) for 30 min and then cooled in an ice-water bath. The respective primary amine (3 equiv) diluted in THF (25 mL) was added dropwise. After which the water bath was removed and the reaction mixture was shaken at rt for 12 h. The resin were then filtered and washed with DMF (20 mL x 3), H_2O (20 mL x 3), EtOH (20 mL x 3), CH_2Cl_2 (20 mL x 3), Et_2O (20 mL x 3) and dried overnight at 50 °C in a vacuum oven.

2.4.2.9 Preparation of benzyl 2-(*N*-substituted-*N'*-cyanoformamidino)acetate resin (2-2-4)

Resin **2-2-3** (2.2698 g, 2.8 mmol) was swollen in THF (15 mL) for 30 min and then cooled in an ice-water bath. Ethoxymethylene cyanamide (0.8236 g, 8.4 mmol) in THF (15 mL) was added dropwise and the reaction mixture was shaken at rt for 12 h. After which, the resin was filtered and washed with DMF (20 mL x 3), H_2O (20 mL x 3), EtOH (20 mL x 3), CH_2Cl_2 (20 mL x 3), Et_2O (20 mL x 3) and dried overnight at 50 °C in a vacuum oven.

2.4.2.10 Preparation of benzyl 2-(*N*-substituted-*N'*-cyanoacetamidino)acetate resin (2-2-4) (R^2=CH_3)

Resin **2-2-3** (2.2551 g, 2.8 mmol) was swollen in THF (20 mL) for 30 min and then cooled in

an ice-water bath. DBU (1.066 g, 14 mmol) was added followed by dropwise addition of methyl ethoxymethylene cyanamide (0.9416 g, 8.4 mmol) in THF (15 mL). After which, the reaction mixture was shaken at rt for 12 h. The resin was then filtered and washed with DMF (20 mL x 3), H_2O (20 mL x 3), EtOH (20 mL x 3), CH_2Cl_2 (20 mL x 3), Et_2O (20 mL x 3) and dried overnight at 50 °C in a vacuum oven.

2.4.2.11 Preparation of benzyl 2-(*N*-substituted-*N'*-cyanobenzamidino)acetate resin (2-2-4) (R^2=Ph)

Resin **2-2-3** (2.2551 g, 2.8 mmol) was swollen in THF (20 mL) for 30 min and then cooled in an ice-water bath. DBU (1.066 g, 14 mmol) was added, followed by addition of phenyl ethoxymethylene cyanamide (1.463 g, 8.4 mmol) in THF (15 mL). After which, the reaction mixture was refluxed for 12 h. The resin was then filtered and washed with DMF (20 mL x 3), H_2O (20 mL x 3), EtOH (20 mL x 3), CH_2Cl_2 (20 mL x 3), Et_2O (20 mL x 3) and dried overnight at 50 °C in a vacuum oven.

2.4.2.12 Preparation of benzyl 5-amino-(3-substituted)-imidazole-4-carboxylate resin (2-2-5)

Resin **2-2-4** (2.2876 g, 2.8 mmol) was swollen in DMF (15 mL) for 30 min then cooled in an ice-water bath. KO^{t}Bu (0.6284 g, 5.6 mmol) in ^{t}BuOH (15 mL) was added and the reaction mixture was stirred at rt for 2 h. After which, the reaction mixture was quenched with NH_4Cl and the resin were filtered, washed with DMF (20 mL x 3), H_2O (20 mL x 3), EtOH (20 mL x 3), CH_2Cl_2 (20 mL x 3), Et_2O (20 mL x 3) and dried overnight at 50 °C in a vacuum oven.

2.4.2.13 Preparation of benzyl 5-(3-substitutedureido)-imidazole-4-carboxylate resin (2-2-6)

2-2-5 (0.3054 g, 0.3756 mmol) was swollen in *o*-xylene (10 mL) for 30 min. Isocyanate (3 equiv) was added and the reaction mixture was heated at 120-125 °C for 24 h. The resin was filtered, washed with DMF (20 mL x 3), H_2O (20 mL x 3), EtOH (20 mL x 3), CH_2Cl_2 (20 mL x 3), Et_2O (20 mL x 3) and dried overnight at 50 °C in a vacuum oven.

2.4.2.14 Preparation of 1,7- or 1,7,8-substituted xanthines (2-2-7)

THF (6 mL), MeOH (3 mL), and NaOEt (21% (w/w) in denatured EtOH, 0.42 mL, 1.1268 mmol) were added to resin **2-2-6** (0.3249 g, 0.3756 mmol) and the reaction mixture was refluxed at 90 °C for 2 h. After which, the reaction mixture was filtered and the resin washed with MeOH (10 mL x 3) and CH_2Cl_2 (10 mL x 3). The combined organic layer was concentrated and purified by CC (EtOAc:hexane = 2:1 then MeOH:CH_2Cl_2 = 1:10) to give **2-2-7**.

2.4.2.15 Preparation of 1,3,7- or 1,3,7,8-substituted xanthines (2-2-7)

THF (6 mL), MeOH (3 mL), and NaOEt (21% (w/w) in denatured EtOH, 0.42 mL, 1.1268 mmol) were added to **2-2-6** (0.3249 g, 0.3756 mmol) and the mixture was refluxed at 90 °C for 2 h. After which, the mixture was concentrated and THF (8 mL), DIEA (5 equiv) and the respective halide (3 equiv) were added. The reaction mixture was stirred at rt for 12 h and filtered. The resin was washed with MeOH (10 mL x 3), CH_2Cl_2 (10 mL x 3) and the combined organic layer was concentrated and purified by CC (EtOAc:hexane = 2:1 then MeOH:CH_2Cl_2 = 1:10) to give **2-2-7**.

2-2-7b: 1-Allyl-7-butylxanthine. ^{1}H NMR ($CDCl_3$): δ 10.40 (s, *NH*, 1H), 7.60 (s, *CH*, 1H), 6.00-5.87 (m, NCH_2CHCH_2, 1H), 5.30-5.18 (m, NCH_2CHCH_2, 2H), 4.62-4.60 (d, *J* = 5.58 Hz, NCH_2CHCH_2**,** 2H), 4.31-4.26 (t, *J* = 7.14 Hz, $NCH_2CH_2CH_2CH_3$, 2H), 1.91-1.81 (m, $NCH_2CH_2CH_2CH_3$, 2H), 1.42-1.30 (m, $NCH_2CH_2CH_2CH_3$, 2H), 0.99-0.94 (t, *J* = 7.49 Hz, $NCH_2CH_2CH_2CH_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 155.1, 151.1, 147.3, 141.0, 132.1, 117.5, 107.0, 47.1, 42.8, 32.7, 19.6, 13.5; Mass spectrum (EI) m/z 248.2 (M^+) Exact mass calcd for $C_{12}H_{16}N_4O_2$: m/z 248.1273; found 248.1272.

2-2-7c: 7-Butyl-1-phenylxanthine. ^{1}H NMR ($CDCl_3$): δ 7.70 (s, *CH*, 1H), 7.54-7.41 (m, *ArH*, 3H), 7.29-7.26 (m, *ArH*, 2H), 4.28-4.23 (t, *J* = 7.31 Hz, $NCH_2CH_2CH_2CH_3$**,** 2H), 1.90-1.80 (m, $NCH_2CH_2CH_2CH_3$, 2H), 1.41-1.31 (m, $NCH_2CH_2CH_2CH_3$, 2H), 0.96-0.91 (t, *J* = 7.31 Hz, $NCH_2CH_2CH_2CH_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 155.5, 151.5, 147.9, 141.3, 134.9, 129.4, 129.2, 128.8, 107.2, 42.2, 32.7, 19.6, 13.4; Mass spectrum (EI) m/z 283.9 (M^+) Exact mass calcd for $C_{15}H_{16}N_4O_2$: m/z 284.1273; found 284.1270.

2-2-7d: 1-Benzyl-7-butylxanthine. ^{1}H NMR ($CDCl_3$): δ 10.55 (s, *NH*, 1H), 7.60 (s, *CH*, 1H), 7.50-7.47 (m, *ArH*, 2H), 7.32-7.24 (m, *ArH*, 3H), 5.17 (s, $ArCH_2$, 2H), 4.30-4.25 (t, *J* = 7.14 Hz, $NCH_2CH_2CH_2CH_3$**,** 2H), 1.90-1.80 (m, $NCH_2CH_2CH_2CH_3$, 2H), 1.41-1.29 (m, $NCH_2CH_2CH_2CH_3$, 2H), 0.98-0.93 (t, *J* = 7.31 Hz, $NCH_2CH_2CH_2CH_3$**,** 3H); ^{13}C NMR ($CDCl_3$): δ 155.4, 151.4, 147.3, 141.0, 137.2, 128.8, 128.4, 127.5, 107.0, 47.0, 43.9, 32.7, 19.5, 13.5; Mass spectrum (EI) m/z 298.2 (M^+) Exact mass calcd for $C_{16}H_{18}N_4O_2$: m/z 298.1430; found 298.1435.

2-2-7e: 7-Benzyl-1-hexylxanthine. ^{1}H NMR ($CDCl_3$): δ 11.26 (s, *NH*, 1H), 7.62 (s, *CH*, 1H), 7.44-7.35 (m, *ArH*, 5H), 5.48 (s, $ArCH_2$, 2H), 3.99-3.94 (t, *J* = 7.31 Hz,

N*CH*$_2$CH$_2$CH$_2$CH$_2$CH$_3$, 2H), 1.64-1.62 (m, NCH$_2$*CH*$_2$CH$_2$CH$_2$CH$_2$CH$_3$, 2H), 1.31-1.25 (m, NCH$_2$CH$_2$*CH*$_2$*CH*$_2$*CH*$_2$CH$_3$, 6H), 0.89-0.85 (t, *J* = 6.09 Hz, *CH*$_3$, 3H); ^{13}C NMR (CDCl$_3$): δ 155.7, 151.4, 147.2, 140.8, 134.9, 129.1, 128.7, 128.2, 107.0, 50.3, 40.9, 31.5, 28.0, 26.6, 22.5, 14.0; Mass spectrum (EI) m/z 326.0 (M^+) Exact mass calcd for $C_{18}H_{22}N_4O_2$: m/z 326.1743; found 326.1740.

2-2-7f: 7-Benzyl-1-phenylxanthine. ^{1}H NMR (CDCl$_3$): δ 11.47 (s, *NH*, 1H), 7.69 (s, *CH*, 1H), 7.53-7.25 (m, *ArH*, 10H), 5.44 (s, *CH*$_2$, 2H); ^{13}C NMR (CDCl$_3$): δ 155.7, 151.4, 147.8, 141.2, 134.8, 134.7, 129.3, 129.1, 128.8, 128.8, 128.4, 107.1, 50.5; Mass spectrum (EI) m/z 318.0 (M^+) Exact mass calcd for $C_{18}H_{14}N_4O_2$: m/z 318.1117; found 318.1118.

2-2-7g: 1,7-Dibenzylxanthine. ^{1}H NMR (DMSO-*d*$_6$): δ 8.21 (s, CH, 1H), 7.33-7.26 (m, *ArH*, 10H), 5.46 (s, N*CH*$_2$, 2H), 4.99 (s, N*CH*$_2$, 2H); ^{13}C NMR (DMSO-*d*$_6$): δ 155.0, 150.9, 148.0, 143.1, 137.7, 137.0, 128.7, 128.2, 128.0, 127.5, 127.3, 127.0, 105.7, 48.9, 42.8; Mass spectrum (EI) m/z 331.9 (M^+) Exact mass calcd for $C_{19}H_{16}N_4O_2$: m/z 332.1273; found 332.1274.

2-2-7h: 1-Allyl-7-benzylxanthine. ^{1}H NMR (CDCl$_3$): δ 11.60 (s, *NH*, 1H), 7.63 (s, *CH*, 1H), 7.40-7.33 (m, *ArH*, 5H), 5.99-5.79 (m, NCH$_2$*CH*CH$_2$, 1H), 5.48 (s, N*CH*$_2$, 2H), 5.28-5.09 (m, NCH$_2$CH*CH*$_2$, 2H), 4.61-4.59 (d, *J* = 5.58 Hz, N*CH*$_2$CHCH$_2$, 2H); ^{13}C NMR (CDCl$_3$): δ 155.3, 151.2, 147.5, 141.0, 135.3, 132.1, 129.1, 128.8, 128.2, 117.4, 106.9, 50.4, 42.7; Mass spectrum (EI) m/z 282.0 (M^+) Exact mass calcd for $C_{15}H_{14}N_4O_2$: m/z 282.1117; found 282.1115.

2-2-7i: 7-Benzyl-3-methyl-1-phenylxanthine. ^{1}H NMR (CDCl$_3$): δ 7.55 (s, *CH*, 1H), 7.46-7.16 (m, *ArH*, 10H), 5.40 (s, *CH*$_2$, 2H), 3.54 (s, *CH*$_3$, 3H); ^{13}C NMR (CDCl$_3$): δ 155.2, 151.6,

149.5, 141.1, 135.4, 129.4, 129.1, 128.7, 128.2, 107.2, 50.4, 29.8; Mass spectrum (EI) m/z 332.0 (M^+) Exact mass calcd for $C_{19}H_{16}N_4O_2$: m/z 332.1273; found 332.1274.

2-2-7j: 7-Benzyl-1-phenyl-3-propargylxanthine. ^{1}H NMR ($CDCl_3$): δ 7.65 (s, *CH*, 1H), 7.53-7.25 (m, *ArH*, 10H), 5.47 (s, N*CH*$_2$, 2H), 4.91-4.90 (d, *J* = 2.46 Hz, N3*CH*$_2$CCH, 2H), 2.28-2.27 (t, *J* = 2.43 Hz, CH_2C*CH*, 1H); ^{13}C NMR ($CDCl_3$): δ 155.0, 150.7, 148.2, 141.3, 135.1, 134.9, 129.4, 129.1, 128.8, 128.7, 128.4, 107.4, 72.0, 50.5, 32.6; Mass spectrum (EI) m/z 356.0 (M^+) Exact mass calcd for $C_{21}H_{16}N_4O_2$: m/z 356.1273; found 356.1272.

2-2-7k: 1-Allyl-7-benzyl-3-methylxanthine. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 (s, *CH*, 1H), 7.38-7.32 (m, *ArH*, 5H), 5.96-5.88 (m, NCH_2*CH*CH_2, 1H), 5.49 (s, N*CH*$_2$, 2H), 5.28-5.17 (m, NCH_2CH*CH*$_2$, 2H), 4.63-4.62 (m, N*CH*$_2$, 2H), 3.57 (s, N*CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 154.8, 151.2, 149.0, 140.9, 135.2, 132.3, 129.1, 128.7, 128.0, 117.5, 107.0, 50.3, 43.4, 29.7; Mass spectrum (EI) m/z 296.0 (M^+) Exact mass calcd for $C_{16}H_{16}N_4O_2$: m/z 296.1273; found 296.1280.

2-2-7l: 1-Allyl-7-benzyl-3-propargylxanthine. ^{1}H NMR ($CDCl_3$, 500 MHz) : δ 7.58 (s, *CH*, 1H), 7.39-7.33 (m, *ArH*, 5H), 5.96-5.88 (m, NCH_2*CH*CH_2, 1H), 5.49 (s, N*CH*$_2$, 2H), 5.29-5.18 (m, NCH_2CH*CH*$_2$, 2H), 4.88-4.87 (d, *J* = 1.90 Hz, N*CH*$_2$CCH, 2H), 4.64-4.62 (m, N*CH*$_2$$CHCH_2$, 2H), 2.25-2.25 (t, *J* = 2.20 Hz, NCH_2C*CH*, 1H); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 154.7, 150.4, 147.7, 141.1, 135.0, 132.0, 129.1, 128.7, 128.2, 117.8, 107.2, 77.6, 71.8, 50.4, 43.5, 32.5; Mass spectrum (EI) m/z 320.0 (M^+) Exact mass calcd for $C_{18}H_{16}N_4O_2$: m/z 320.1273; found 320.1275.

2-2-7m: 7-Benzyl-1,3-diallylxanthine. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 (s, *CH*, 1H), 7.38-7.33 (m, *ArH*, 5H), 6.00-5.88 (m, NCH_2*CH*CH_2, 2H), 5.49 (s, N*CH*$_2$, 2H), 5.32-5.19 (m,

$NCH_2CH\mathit{CH_2}$, 4H), 4.71-4.62 (m, $N\mathit{CH_2}CHCH_2$, 4H); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 154.8, 150.7, 148.5, 141.0, 135.1, 132.2, 131.5, 129.1, 128.7, 128.1, 118.0, 117.5, 107.0, 50.3, 45.3, 43.3; Mass spectrum (EI) m/z 321.8 (M^+) Exact mass calcd for $C_{18}H_{18}N_4O_2$: m/z 322.1430; found 322.1435.

2-2-7n: 1-Allyl-3,7-dibenzylxanthine. ^1H NMR ($CDCl_3$): δ 7.46 (s, *CH*, 1H), 7.42-7.41 (m, *ArH*, 2H), 7.29-7.14 (m, *ArH*, 8H), 5.91-5.78 (m, $NCH_2\mathit{CH}CH_2$, 1H), 5.40 (s, $N\mathit{CH_2}$, 2H), 5.19-5.08 (m, $N\mathit{CH_2}$ and $NCH_2CH\mathit{CH_2}$, 4H), 4.56-4.54 (m, $N\mathit{CH_2}CHCH_2$, 2H); ^{13}C NMR ($CDCl_3$): δ 154.8, 151.0, 148.7, 140.9, 136.4, 135.1, 132.2, 129.1, 128.7, 128.5, 128.2, 127.8, 117.5, 107.1, 50.3, 46.6, 43.4; Mass spectrum (EI) m/z 371.7 (M^+) Exact mass calcd for $C_{22}H_{20}N_4O_2$: m/z 372.1586; found 372.1584.

2-2-7o: 3-Allyl-7-benzyl-1-phenylxanthine. ^1H NMR ($CDCl_3$): δ 7.54 (s, *CH*, 1H), 7.45-7.17 (m, *ArH*, 10H), 6.00-5.87 (m, $NCH_2\mathit{CH}CH_2$, 1H), 5.40 (s, $N\mathit{CH_2}$, 2H), 5.30-5.15 (m, $NCH_2CH\mathit{CH_2}$, 2H), 4.67-4.65 (d, *J* = 5.91 Hz, $N\mathit{CH_2}CHCH_2$, 2H); ^{13}C NMR ($CDCl_3$): δ 155.2, 151.1, 149.0, 141.2, 135.3, 135.0, 131.4, 129.3, 129.1, 128.7, 128.7, 128.4, 118.6, 107.3, 50.4, 45.6; Mass spectrum (EI) m/z 358.1 (M^+) Exact mass calcd for $C_{21}H_{18}N_4O_2$: m/z 358.1430; found 358.1422.

2-2-7p: 3,7-Dibenzyl-1-phenylxanthine. ^1H NMR ($CDCl_3$): δ 7.54-7.15 (m, *CH* and *ArH*, 16H), 5.36 (s, $N\mathit{CH_2}$, 2H), 5.20 (s, NCH_2, 2H); ^{13}C NMR ($CDCl_3$): δ 155.1, 151.4, 149.1, 141.0, 136.2, 135.3, 135.0, 129.3, 129.2, 129.1, 128.7, 128.6, 128.5, 128.4, 127.9, 107.3, 50.3, 46.7; Mass spectrum (EI) m/z 408.1 (M^+) Exact mass calcd for $C_{25}H_{20}N_4O_2$: m/z 408.1586; found 408.1588.

2-2-7q: 1-Allyl-7,8-dimethylxanthine. ^1H NMR (DMSO-d_6): δ 11.76 (s, *NH*, 1H), 5.90-5.75

(m, NCH_2CHCH_2, 1H), 5.08-5.00 (m, NCH_2CHCH_2, 2H), 4.42-4.40 (d, J = 4.89 Hz, NCH_2CHCH_2, 2H), 3.78 (s, NCH_3, 3H), 2.36 (s, CCH_3, 3H); ^{13}C NMR (DMSO-d_6): δ 154.0, 151.0, 150.0, 146.3, 132.8, 115.4, 105.8, 41.0, 30.8, 12.2; Mass spectrum (EI) m/z 219.9 (M^+) Exact mass calcd for $C_{10}H_{12}N_4O_2$: m/z 220.0960; found 220.0960.

2-2-7r: 7,8-Dimethyl-1-phenylxanthine. ^{1}H NMR (DMSO-d_6): δ 11.85 (s, *NH*, 1H), 7.48-7.21 (m, *ArH*, 5H), 3.76 (s, NCH_3, 3H), 2.39 (s, CCH_3, 3H); ^{13}C NMR (DMSO-d_6): δ 155.0, 151.6, 150.9, 147.2, 136.0, 129.4, 128.7, 127.8, 106.6, 31.3, 12.7; Mass spectrum (EI) m/z 255.9 (M^+) Exact mass calcd for $C_{13}H_{12}N_4O_2$: m/z 256.0960; found 256.0960.

2-2-7s: 1-Allyl-3-benzyl-7,8-dimethylxanthine. ^{1}H NMR ($CDCl_3$): δ 7.41-7.17 (m, *ArH*, 5H), 5.90-5.72 (m, NCH_2CHCH_2, 1H), 5.23-5.03 (m, ArCH_2 and NCH_2CHCH_2, 4H), 4.54-4.53 (d, J = 5.58 Hz, NCH_2CHCH_2, 2H), 3.81 (s, NCH_3, 3H), 2.38 (s, CCH_3, 3H); ^{13}C NMR ($CDCl_3$): δ 154.8, 151.0, 150.8, 147.8, 136.6, 132.5, 128.6, 128.4, 127.7, 117.2, 107.5, 46.4, 43.2, 31.8, 13.1; Mass spectrum (EI) m/z 310.2 (M^+) Exact mass calcd for $C_{17}H_{18}N_4O_2$: m/z 310.1430; found 310.1430.

2-2-7t: 1-Phenyl-3,7,8-trimethylxanthine. ^{1}H NMR ($CDCl_3$): δ 7.46-7.16 (m, *ArH*, 5H), 3.82 (s, NCH_3, 3H), 3.52 (s, NCH_3, 2H), 2.42 (s, CCH_3, 3H); ^{13}C NMR ($CDCl_3$): δ 155.2, 151.7, 151.1, 148.6, 135.7, 129.3, 128.8, 128.6, 107.7, 31.9, 29.7, 13.1; Mass spectrum (EI) m/z 270.1 (M^+) Exact mass calcd for $C_{14}H_{14}N_4O_2$: m/z 270.1117; found 270.1110.

2-2-7u: 1-Allyl-7-methyl-8-phenylxanthine. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.26 (s, *NH*, 1H), 7.71-7.53 (m, *ArH*, 5H), 5.99-5.91 (m, NCH_2CHCH_2, 1H), 5.30-5.19 (m, NCH_2CHCH_2, 2H), 4.65-4.63 (m, NCH_2CHCH_2, 2H), 4.06 (s, CH_3, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 155.6, 152.5, 151.1, 146.7, 132.2, 130.5, 129.3, 128.9, 128.0, 117.4, 108.5, 42.7, 33.9; Mass

spectrum (ESI) m/z 283.1 ($M+H^+$) Exact mass calcd for $C_{15}H_{14}N_4O_2$: m/z 282.1117; found 283.1190 ($M+H^+$).

2-2-7v: 1-Allyl-3,7-dimethyl-8-phenylxanthine. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.69-7.52 (m, *ArH*, 5H), 5.99-5.91 (m, NCH_2CHCH_2, 1H), 5.31-5.19 (m, NCH_2CHCH_2, 2H), 4.67-4.66 (m, NCH_2CHCH_2, 2H), 4.06 (s, NCH_3, 3H), 3.63 (s, NCH_3, 3H); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 155.2, 152.2, 151.3, 148.5, 132.4, 130.4, 129.2, 128.9, 128.4, 117.4, 108.6, 43.3, 33.9, 29.7; Mass spectrum (ESI) m/z 297.1 ($M+H^+$) Exact mass calcd for $C_{16}H_{16}N_4O_2$: m/z 296.1273; found 297.1346 ($M+H^+$).

2.5 References

[1] (a) Dorfman, L. J.; Jarvik, M. E. *Clin. Pharmacol. Ther.* **1970**, *11*, 869-872. (b) Wang, Y.; Chackalamannil, S.; Hu, Z.; Boyle, C. D.; Lankin, C. M.; Xia, Y.; Xu, R.; Asberom, T.; Pissarnitski, D.; Stamford, A. W.; Greenlee, W. J.; Skell, J.; Kurowski, S.; Vemulapalli, S.; Palamanda, J.; Chintala, M.; Wu, P.; Myers, J.; Wang, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3149-3152. (c) Strappaghetti, G.; Corsano, S.; Barbaro, R.; Giannaccini, G.; Betti, L. *Bioorg. Med. Chem.* **2001**, *9*, 575-583. (d) Schweighoffer, F.; Guillet, P. *U.S. Patent 2005043319*, 2005. (e) Daly, J. W.; Hide, I.; Müller, C. E.; Shamim, M. *Pharmacology* **1991**, *42*, 309-321. (f) Jacobsen, K. A.; van Galen, P. J. M.; Williams, M. *J. Med. Chem.* **1992**, *35*, 407-422. (g) Chappe, V.; Mettey, Y.; Vierfond, J. M.; Hanrahan, J. W.; Gola, M.; Verrier, B.; Becq, F. *Brit. J. Pharmacol.* **1998**, *123*, 683-693.

[2] DeSarro, A.; Grasso, S.; Zappalà, M.; Nava, F.; DeSarro, G. *Arch. Pharmacol.* **1997**, *356*, 48-55.

[3] (a) Dawe, R. A.; Parkin, C.; Kerr, J. S.; Hindmarch, I. *Med. Sci. Res.* **1995**, *23*, 335-336. (b) Kase, H.; Nakagawa, Y.; Shiozaki, S.; Kobayashi, M.; Toki, S.; Seno, N.; Ikeda, K. WO2005056016, **2005**.

[4] (a) Takeuchi, M.; Takayama, M.; Shirakura, S.; Kase, H. WO2005072739, **2005**. (b) Pinto, I. L.; Rahman, S. S.; Nicholson, N. H. WO2005077950, **2005**. (c) Yasui, K.; Komiyama, A. *Int. J. Hematol.* **2001**, *73*, 87-92.

[5] Traube,W. *Chem. Ber.* **1900**, *33*, 3035-3056.

[6] (a) Zavialov, I. A.; Dahanukar, V. H.; Nguyen, H.; Orr, C.; Andrews, D. R. *Org. Lett.*

2004, *6*, 2237-2240. (b) Kramer, G. L.; Garst, J. E.; Mitchel, S. S.; Wells, J. N. *Biochemistry* **1977**, *16*, 3316-3321. (c) Hayallah, A. M.; Ramírez, J. S.; Reith, U.; Schobert, U.; Preiss, B.; Schumacher, B.; Daly, J. W.; Müller, C. E. *J. Med. Chem.* **2002**, *45*, 1500-1510. (d) Hirokazu, S.; Manabu, Y.; Susumu, S.; Ken-ichi, M.; Kenji, Y.; Hiroyuki, S. *Chem. Pharm. Bull.* **2002**, *50*, 1163-1168. (e) Bridson, P. K.; Wang, X. D. *Synthesis* **1995**, 855-858.

[7] (a) Speer, J. H.; Raymond, A. L. *J. Am. Chem. Soc.* **1953**, *75*, 114-115. (b) Kim, H.; Ji, X.; Melman, N.; Olah, M. E.; Stiles, G.. L.; Jacobson, K. A. *J. Med. Chem*. **1994**, *37*, 3373-3382. c) Grundmann, C.; Kreutzberger, A. *J. Am. Chem. Soc*. **1955**, *77*, 6559-6562. (d) Müller, C. E. *Synthesis* **1993**, 125-128. e) Kim, S.-A.; Marshall, M. A.; Melman, N.; Kim, H. S.; Müller, C. E.; Linden, J.; Jacobson, K.A. *J. Med. Chem*. **2002**, *45*, 2131-2138.

[8] Beer, D.; Bhalay, G.; Dunstan, A.; Glen, A.; Haberthuer, S. Moser, H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1973-1976.

[9] (a) Boeckman Jr., R. K.; Starrett Jr., J. E.; Nickell, D. G.; Sum, P. E. *J. Am. Chem. Soc.* **1986**, *108*, 5549-5559. (b) Spaller, M. R.; Thielemann, W. T.; Brennan, P. E.; Bartlett, P. A. *J. Comb. Chem.* **2002**, *4*, 516-522.

[10] Asberom, T.; Clader, J. W.; Hu, Y. Q.; Pissarnitski, D. A.; Stamford, A.; Xu, R. WO 2003042216, **2003**.

[11] (a) Hergueta, A. R.; Figueira, M. J.; López, C.; Caamano, O.; Fernández, F.; Rodríguez-Borges, J. E. *Chem. Pharm. Bull.* **2002**, *50*, 1379-1382. (b) Sanemitsu, Y.; Nakayama, Y. *Synthesis* **1984**, 770-771.

[12] (a) Kearney, P. C.; Fernandez, M.; Flygare, J. A. *J. Org. Chem.* **1998**, *63*, 196-200. (b) Bilodeau, M. T.; Cunningham, A. M. *J. Org. Chem.* **1998**, *63*, 2800-2801. (c) Swayze, E. E. *Tetrahedron Lett.* **1997**, *38*, 8465-8468.

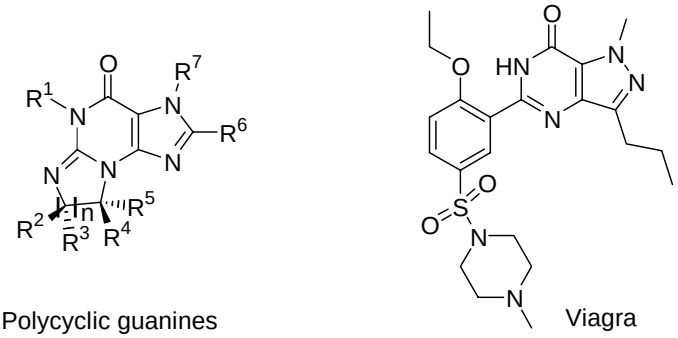
Chapter 3 Combinatorial Solution-Phase Synthesis of Polycyclic Guanines

3.1 Introduction

3.1.1 Importance of polycyclic guanines

Phosphodiesterase (PDE) V inhibitor compounds inhibit the PDE V isoenzyme, and therefore are of potential pharmaceutical and therapeutic interest.[1] One example is Viagra (Pfizer, NY), which is used for treating erectile dysfunction (impotency).[2] Polycyclic guanines are an important class of PDE V inhibitors for treating urological, vascular or pulmonary disorders.[2] Figure 3-1 shows the general structure of polycyclic guanines.

Figure 3-1 Structures of Polycyclic Guanines and Viagra

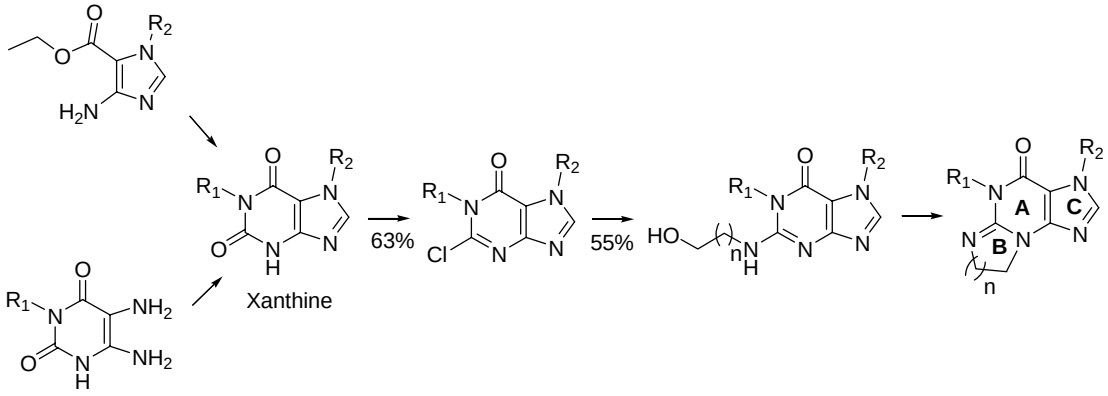


3.1.2 General methods for solution-phase synthesis of polycyclic guanines

Many methods have been reported for the synthesis of polycyclic guanines.[2a,3] Most of them employ xanthine as the key intermediate, which can be prepared from 4-amino-5-alkoxycarbonylimidazole or substituted 5,6-diamino uracil (Scheme 3-1).[2a,3a-3f] In these methods, xanthine is chlorinated at the C2-position and then reacted with amino alcohol to give a precursor, which is subsequently cyclized to afford the polycyclic guanines. Chlorination and the accompanying substitution reactions generally occur with moderate yields (Scheme 3-1), which makes these multi-step syntheses less attractive for library generation in pharmaceutical research. Although some modifications, such as using

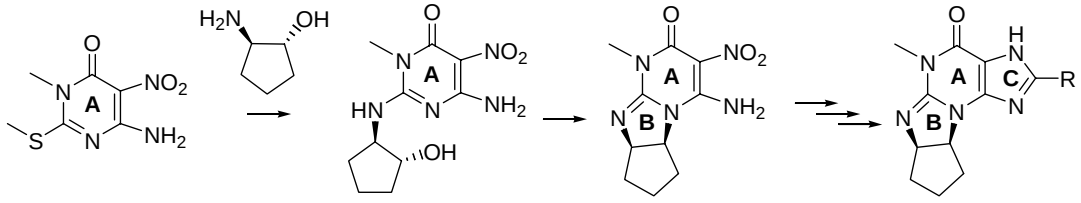
thioxanthine as the intermediate, have been developed, the yields for the ring C construction were even poorer.[3g]

Scheme 3-1 Synthesis of Polycyclic Guanines via 2-Chloropurine



Besides the aforementioned methods, another reported synthesis involves building rings A and B prior to ring C (Scheme 3-2).[3h] In this synthesis, a thiomethyl pyrimidine was reacted with an amino alcohol to give an intermediate which was cyclized to complete the construction of rings A and B. Subsequent ring C formation afforded the polycyclic guanines. Although this is a novel route, the preparation of the thiomethyl pyrimidine was rather complicated and the average yield for each reaction step was lower than the above mentioned methods.

Scheme 3-2 Synthesis of Polycyclic Guanines via Thiomethyl Pyrimidine



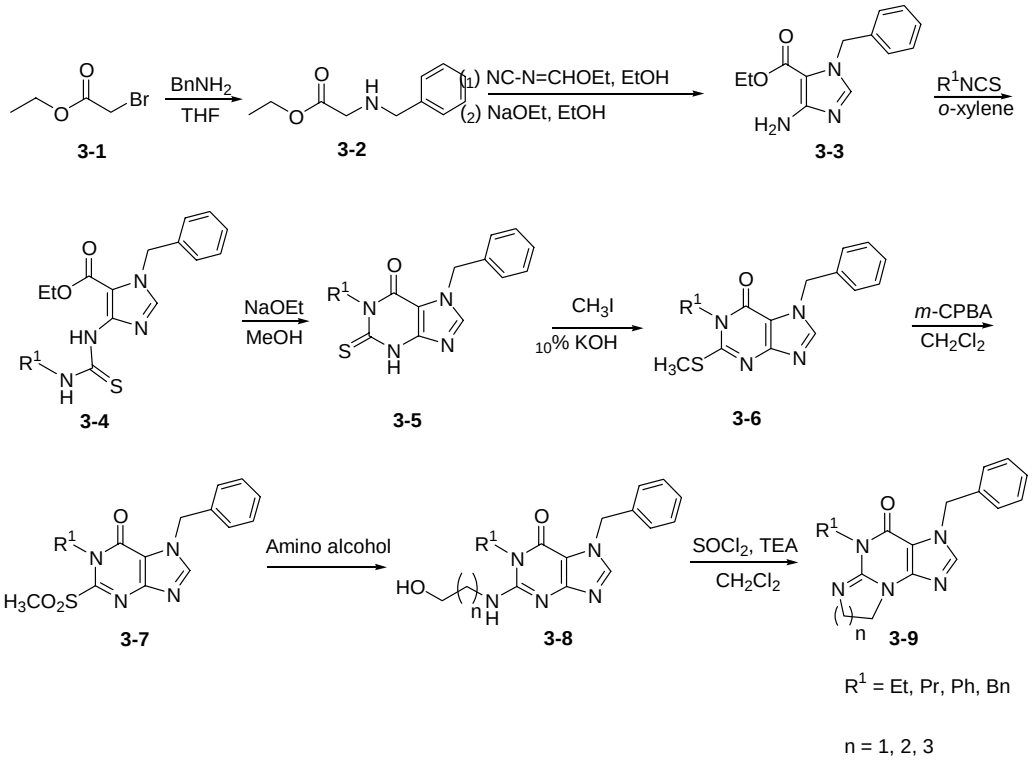
3.1.3 Objectives and scope of this study

This project aims to develop an alternative synthetic route to polycyclic guanines which would be applicable to combinatorial synthesis and library generation.

3.2 Results and Discussion

Since low yields were obtained during the chlorination of xanthines,[3] we decided that using a thioxanthine as an intermediate would be a preferred choice. This is because S-alkylation of the thioxanthine would readily give a sulfide that can be oxidized to the corresponding sulfone, which is an activated leaving group.

Scheme 3-3 Combinatorial Solution-Phase Synthesis of Polycyclic Guanines



3-1 **3-2** **3-3** **3-4** **3-5** **3-6** **3-7** **3-8** **3-9**

3.2.1 Synthesis of 2-thioxanthines (3-5)

To begin our investigation, we had to prepare 2-thioxanthines (**3-5**) whose synthesis have been developed in our previous study.[4] As shown in Scheme 3-3, ethyl bromoacetate (**3-1**) was reacted with benzyl amine in THF to afford ethyl *N*-benzyl glycinate (**3-2**) in 93% yield. Compound **3-2** was then treated with ethoxymethylene cyanamide to give an intermediate which was cyclized with NaOEt in an one-pot reaction to give ethyl 5-amino-3-benzyl-3*H*-imidazole-4-carboxylate (**3-3**) in 86% overall yield. Treatment of

compound **3-3** with isothiocyanates in *o*-xylene (140 ºC, 24 h) provided **3-4** in good yield. Subsequent ring closure of **3-4** with NaOEt/MeOH afforded 1,7-substituted 2-thioxanthines **3-5** in quantitative yield.

3.2.2 Synthesis of 7-benzyl-2-(methylthio)-1-substituted-1*H*-purin-6(7*H*)-one (3-6)

A typical S-alkylation was performed in DMF or THF in the presence of a base.[5] However Kang has reported a S-alkylation of thiopyrimidine using 10% KOH solution and diethyl sulfate.[6] The product formed precipitated from the solution so that only a filtration was needed for purification. We thought that this method could be adopted for the synthesis of **3-6**, as compound **3-5** also contained a similar thiopyrimidine structure. Hence, by applying Kang's protocol, **3-6** was successfully prepared in quantitative yield. The reaction proceeded rapidly at room temperature and the product was collected in pure form by filtration and washing with H_2O.

3.2.3 Synthesis of 7-benzyl-2-(methylsulfonyl)-1-substituted-1*H*-purin-6(7*H*)-one (3-7)

The oxidation of sulfide **3-6** to sulfone **3-7** was conducted with *m*-CPBA. This reaction was completed in 3 h and gave **3-7** in over 90% yield. It is worth noting that *m*-CPBA should be added slowly to the reaction mixture which should be kept at a low temperature during this addition.

3.2.4 Synthesis of 7-benzyl-2-(hydroxyalkylamino)-1-substituted-1*H*-purin-6(7*H*)-one (3-8)

We had initially considered converting **3-6** directly to **3-8**. However all attempts to do this (Scheme 3-4) failed. Hence **3-8** was prepared by first oxidizing the sulfide group in **3-6** to a sulfone, which is a better leaving group. Compound **3-7** was then converted to **3-8** by

nucleophilic substitution. To optimize this reaction, compound **3-7b** was treated with ethanolamine under various conditions to achieve **3-8b** (Table 3-1). The reaction using a mixture of BuOH and DMSO as solvent gave product **3-8b** and a byproduct in 66% and 34% yields, respectively. The byproduct obtained was analyzed and was found to have been derived from a nucleophilic substitution from BuOH (Entry 1, Table 3-1). Attempts to carry out the reaction in DMF at 80 ºC gave product **3-8b** and the xanthine as byproduct. The formation of xanthine was attributed to the presence of moisture which acted as a nucleophile resulting in the hydrolysis of **3-7b**. When the reaction temperature was raised from 80 ºC to 130 ºC, the reaction time was significantly reduced from 30 h to 2 h, and the yield was improved slightly (Entry 3, Table 3-1). To avoid the formation of the hydrolyzed byproduct, molecular sieves were added to the reaction mixture and this resulted in better yield (Entry 4, Table 3-1). When the reaction was carried out without any solvent, the reaction time was shortened to 30 min, but no improvement to the yield of **3-7b** was observed (Entry 5, Table 3-1). Nevertheless, this method of synthesizing **3-8** from **3-6** via **3-7** was more efficient and gave higher yield than the methods reported earlier.[3]

Having optimized the synthetic route to compound **3-8,** different substrates and amino alcohols were reacted to give various analogs of **3-8** in good yields.

Scheme 3-4 Synthesis of **3-8a**

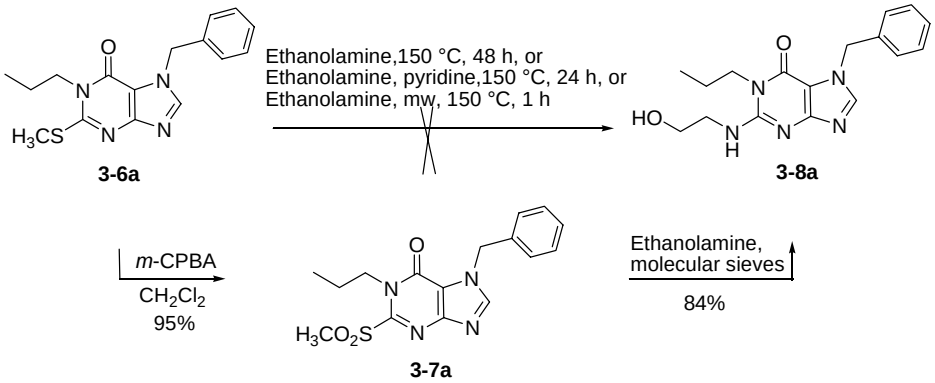


Table 3-1 Synthesis of **3-8a**

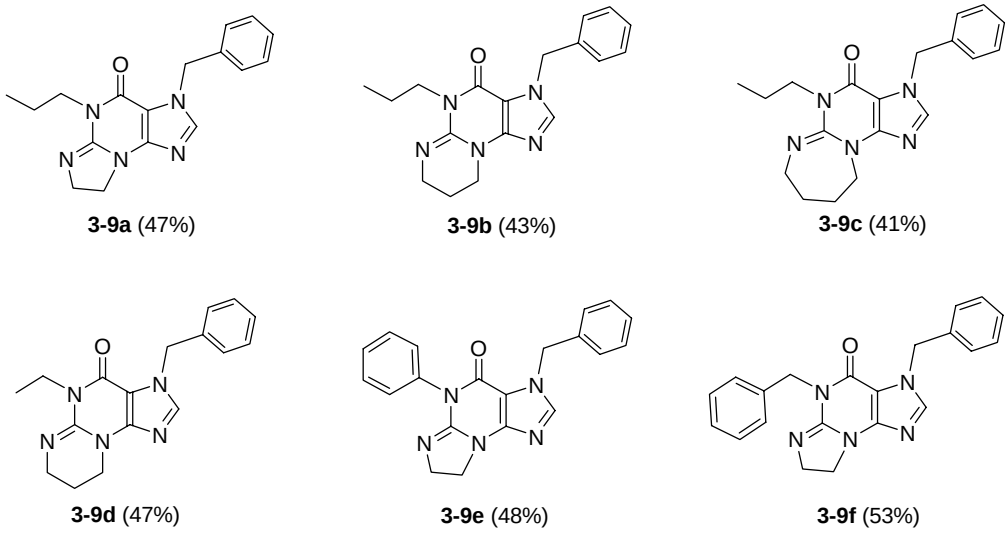
Entry	*Reagent*	*Solvent*	*Conditions*	*Result (Yield)*
1	Ethanolamine	BuOH:DMSO = 4:1	80 ºC, 12 h	p: 66%, byp: 34%
2	Ethanolamine	DMF	80 ºC, 30 h	p: 66%, byp: 34%
3	Ethanolamine	DMF	130 ºC, 2 h	p: 74%, byp: 20%,
4	Ethanolamine with molecular sieves	DMF	130 ºC, 2 h	p: 83%
5	Ethanolamine with molecular sieves	Ethanolamine	130 ºC, 30 min	p: 84%

3.2.5 Synthesis of polycyclic guanines (3-9)

With **3-8** in hand, we proceeded to synthesize the third ring. In all previous reported methods, $SOCl_2$ or CH_3SO_2Cl were used to for this ring formation,[2a,3] and the yields were about 60%. To improve on this methodology, we tried different conditions, such as lowering the temperature or adding the reagent slowly. Eventually we found that the reaction worked well with $SOCl_2$ and TEA in a temperature controlled method (Scheme 3-3). It is important to note that the equivalents of $SOCl_2$ used should be larger than TEA and DIEA gave lower yields than TEA.

To illustrate the versatility of our synthetic route, 6 compounds were prepared (Figure 3-2).

Figure 3-2 Library of Polycyclic Guanines **3-9**



3.3 Conclusion

This study investigated the combinatorial solution-phase parallel synthesis of polycyclic guanines. A highly efficient synthetic route involving 9 steps in total was developed. Unlike previous synthesis of polycyclic guanines which use 2-chloropurine as the necessary intermediate, this method synthesized thioxanthine as the key intermediate. The use of thioxanthine provided a more efficient construction of the third ring. By using parallel synthesis, a set of 6 compounds was prepared. The overall yields of the final products were more than 41%, indicating that the yield for each step was more than 90%.

3.4 Experimental

All chemical reagents were obtained from Aldrich, Merck, Lancaster or Fluka and used without further purification. Analytical TLC was carried out on pre-coated plates (Merck silica gel 60, F254) and visualized with UV light or stained with ninhydrin. CC was

performed with silica (Merck, 70-230 mesh). ^{1}H NMR and ^{13}C NMR spectra were measured at 298 K on a Bruker DPX 300 or DPX 500 Fourier Transform spectrometer. Chemical shifts are reported in δ (ppm), relative to the internal standard of TMS. The signals observed are described as: s, d, t, q, m. The number of protons (n) for a given resonance is indicated as nH. All Infra-red spectra were recorded on a Bio-Rad FTS 165 spectrometer. Mass spectra were performed on VG Micromass 7035 spectrometer under EI, Finnigan/MAT LCQ under ESI (Normal), and Finnigan/MAT 95XL-T under ESI (Accurate).

3.4.1 Synthesis of ethyl *N*-benzyl glycinate (3-2)

Benzylamine (6.55 mL, 60 mmol) was added to ethyl bromoacetate (**3-1**) (2.22 mL, 20 mmol) in THF (100 mL). The mixture was quickly cooled in an ice-water bath and then stirred at rt for 1 h. After which, the reaction mixture was concentrated and purified by CC (EtOAc:hexane = 1:3) to give **3-2** as a colorless oil (3.6 g, 93% yield). ^{1}H NMR ($CDCl_3$): δ 7.35-7.25 (m, *ArH*, 5H), 4.22-4.15 (q, *J* = 7.1 Hz, CH_3CH_2, 2H), 3.84 (s, $ArCH_2$, 2H), 3.42 (s, CH_2, 2H), 2.67 (s, *NH*, 1H), 1.29-1.25 (t, *J* = 7.1 Hz, CH_3CH_2, 3H); ^{13}C NMR ($CDCl_3$): δ 171.9, 138.7, 128.5, 128.4, 127.3, 60.8, 53.0, 49.7, 14.2; Mass spectrum (EI) m/z 193.0 (M^+) Exact mass calcd for $C_{11}H_{15}NO_2$: m/z 193.1103; found 193.1100.

3.4.2 Synthesis of ethyl 5-amino-3-benzyl-3*H*-imidazole-4-carboxylate (3-3)

Compound **3-2** (2 mL, 10.67 mmol) was dissolved in EtOH (10 mL) and the solution was cooled in an ice-water bath. Ethoxymethylene cyanamide (1.119 g, 11.42 mmol) in EtOH (5 mL) was added dropwise and upon completion of addition, the reaction mixture was stirred at rt for 2 h. After which, the reaction mixture was cooled in an ice-water bath and NaOEt (21% (w/w) in denatured EtOH, 4 mL, 10.67 mmol) was added. The reaction mixture was stirred at

rt for another 2 h, concentrated and purified by CC (EtOAc:CH_2Cl_2 = 2:1) to give **3-3** as a colorless solid (2.25 g, 86% yield). ^{1}H NMR ($CDCl_3$): δ 7.22-7.01 (m, *ArH*, 5H), 5.21 (s, Ar*CH*$_2$, 2H), 5.05 (s, *NH*$_2$, 2H), 4.14-4.07 (q, *J* = 7.1 Hz, CH_3*CH*$_2$, 2H), 1.15-1.10 (t, *J* = 7.1 Hz, *CH*$_3$$CH_2$, 3H); ^{13}C NMR ($CDCl_3$): δ 160.5, 155.6, 139.0, 136.5, 128.4, 127.4, 126.6, 101.4, 59.3, 50.3, 14.1; Mass spectrum (EI) m/z 245.1 (M^+) Exact mass calcd for $C_{13}H_{15}N_3O_2$: m/z 245.1164; found 245.1157.

3.4.3 Synthesis of ethyl 3-benzyl-5-(3-alkylthioureido)-3*H*-imidazole-4-carboxylate (3-4)

To compound **3-3** (0.5625 g, 2.29 mmol) was added ethyl isothiocyanate (0.301 mL, 3.44 mmol) and *o*-xylene (6 mL) and the mixture was heated at 140 ºC for 24 h. After which, the mixture was concentrated and purified by CC (EtOAc:hexane = 1:3) to give ethyl 3-benzyl-5-(3-ethylthioureido)-3*H*-imidazole-4-carboxylate (**3-4a**) as a white solid (0.64 g, 85% yield). ^{1}H NMR ($CDCl_3$): δ 10.4 (s, CH_3CH_2*NH*CS, 1H), 9.13 (s, *NH*, 1H), 7.39 (s, *CH*, 1H), 7.25-7.03 (m, *ArH*, 5H), 5.36 (s, Ar*CH*$_2$, 2H), 4.21-4.14 (q, *J* = 7.1 Hz, CH_3*CH*$_2$$CO_2$, 2H), 3.66-3.57 (m, CH_3*CH*$_2$NHCS, 2H), 1.22-1.16 (m, *CH*$_3$, 6H); ^{13}C NMR ($CDCl_3$): δ 177.8, 159.0, 147.1, 137.2, 135.2, 128.4, 127.8, 126.7, 103.5, 60.5, 50.5, 40.1, 13.8, 13.7; Mass spectrum (EI) m/z 332.0 (M^+) Exact mass calcd for $C_{16}H_{20}N_4O_2S$: m/z 332.1307; found 332.1305.

3-4b: Ethyl 3-benzyl-5-(3-propylthioureido)-3*H*-imidazole-4-carboxylate. ^{1}H NMR ($CDCl_3$): δ 10.4 (s, $CH_3CH_2CH_2$*NH*CS, 1H), 9.13 (s, *NH*, 1H), 7.34 (s, *CH*, 1H), 7.27-7.04 (m, *ArH*, 5H), 5.36 (s, Ar*CH*$_2$, 2H), 4.24-4.17 (q, *J* = 7.2 Hz, CH_3*CH*$_2$$CO_2$, 2H), 3.59-3.53 (m, CH_3CH_2*CH*$_2$NHCS, 2H), 1.67-1.55 (m, CH_3*CH*$_2$$CH_2$NHCS, 2H), 1.25- 1.20 (t, *J* = 7.0 Hz, *CH*$_3$$CH_2CO_2$, 3H), 0.93-0.88 (t, *J* = 7.3 Hz, *CH*$_3$$CH_2CH_2$NHCS, 3H); ^{13}C NMR ($CDCl_3$): δ

178.1, 159.2, 147.2, 137.2, 135.2, 128.6, 128.0, 127.0, 103.7, 60.7, 50.7, 47.2, 21.8, 14.0, 11.3; Mass spectrum (EI) m/z 346.1 (M^+) Exact mass calcd for $C_{17}H_{22}N_4O_2S$: m/z 346.1463; found 346.1461. Yield: 83%.

3-4c: Ethyl 3-Benzyl-5-(3-phenylthioureido)-3*H*-imidazole-4-carboxylate. ^{1}H NMR ($CDCl_3$): δ 12.4 (s, Ph*NH*CS, 1H), 9.38 (s, *NH*, 1H), 7.34-7.15 (m, *CH* and *ArH*, 11H), 5.45 (s, Ar*CH*$_2$, 2H), 4.38-4.31 (q, *J* = 7.1 Hz, $CH_3CH_2CO_2$, 2H), 1.38-1.34 (t, *J* = 7.0 Hz, $CH_3CH_2CO_2$, 3H); ^{13}C NMR ($CDCl_3$): δ 177.3, 159.3, 147.0, 138.8, 137.3, 135.2, 128.9, 128.5, 128.4, 127.2, 125.9, 124.4, 104.4, 61.1, 51.0, 14.2; Mass spectrum (EI) m/z 380.2 (M^+) Exact mass calcd for $C_{20}H_{20}N_4O_2S$: m/z 380.1307; found 380.1295. Yield: 89%.

3-4d: Ethyl 3-Benzyl-5-(3-benzylthioureido)-3*H*-imidazole-4-carboxylate. ^{1}H NMR ($CDCl_3$): δ 10.76-10.72 (t, *J* = 5.0 Hz, $ArCH_2$*NH*CS, 1H), 9.21 (s, *NH*, 1H), 7.22-6.94 (m, *CH* and *ArH*, 11H), 5.22 (s, Ar*CH*$_2$, 2H), 4.78-4.76 (d, *J* = 5.2 Hz, Ar*CH*$_2$NHCS, 2H), 4.13-4.06 (q, *J* = 7.2 Hz, $CH_3CH_2CO_2$, 2H), 1.14-1.09 (t, *J* = 7.1 Hz, $CH_3CH_2CO_2$, 3H); ^{13}C NMR ($CDCl_3$): δ 178.3, 158.9, 146.9, 137.2, 137.0, 135.1, 128.3, 128.1, 127.7, 127.1, 126.9, 126.6, 103.5, 60.4, 50.4, 49.0, 13.7; Mass spectrum (EI) m/z 394.2 (M^+) Exact mass calcd for $C_{21}H_{22}N_4O_2S$: m/z 394.1463; found 394.14655. Yield: 90%.

3.4.4 Synthesis of 2-thioxanthines (3-5)

To compound **3-4a** (0.64 g, 1.95 mmol) in MeOH (6 mL) was added NaOEt (21% (w/w) in denatured EtOH, 2 mL, 5.3 mmol). The mixture was refluxed for 2 h then concentrated and the resulting residue was diluted with water (10 mL) and acidified with 1.5 M HCl. The white precipitate which formed was filtered, washed with water and dried to give 7-benzyl-1-ethyl-2-thioxanthine (**3-5a**) as a white power (0.56 g, 99% yield). ^{1}H NMR

(DMSO-d_6): δ 13.52 (s, *NH*, 1H), 8.28 (s, *CH*, 1H), 7.33-7.25 (m, *ArH*, 5H), 5.49 (s, Ar*CH_2*, 2H), 4.45-4.38 (q, *J* = 6.9 Hz, *CH_2*CH_3, 2H), 1.20-1.15 (t, *J* = 6.8 Hz, CH_2*CH_3*, 3H); ^{13}C NMR (DMSO-d_6): δ 173.8, 153.2, 147.6, 143.9, 136.8, 128.7, 127.9, 127.4, 109.3, 49.0, 40.8, 12.0; Mass spectrum (EI) m/z 286.0 (M^+) Exact mass calcd for $C_{14}H_{14}N_4OS$: m/z 286.0888; found 286.0875.

3-5b: 7-Benzyl-1-propyl-2-thioxanthine. ^{1}H NMR (DMSO-d_6): δ 13.51 (s, *NH*, 1H), 8.28 (s, *CH*, 1H), 7.36-7.25 (m, *ArH*, 5H), 5.48 (s, Ar*CH_2*, 2H), 4.33-4.28 (t, *J* = 7.7 Hz, *CH_2*CH_2CH_3, 2H), 1.71-1.59 (m, CH_2*CH_2*CH_3, 2H), 0.88-0.83 (t, *J* = 7.5 Hz, CH_2CH_2*CH_3*, 3H); ^{13}C NMR (DMSO-d_6): δ 174.0, 153.4, 147.7, 143.9, 136.8, 128.7, 127.9, 127.5, 109.2, 49.0, 46.9, 19.7, 11.0; Mass spectrum (EI) m/z 300.1 (M^+) Exact mass calcd for $C_{15}H_{16}N_4OS$: m/z 300.1045; found 300.1039. Yield: 99%.

3-5c: 7-Benzyl-1-phenyl-2-thioxanthine. ^{1}H NMR (DMSO-d_6): δ 13.71 (s, *NH*, 1H), 8.36 (s, *CH*, 1H), 7.47-7.18 (m, *ArH*, 10H), 5.48 (s, Ar*CH_2*, 2H); ^{13}C NMR (DMSO-d_6): δ 175.5, 153.8, 148.3, 143.9, 139.3, 136.7, 129.2, 128.9, 128.7, 128.0, 127.8, 127.6, 109.7, 49.0; Mass spectrum (EI) m/z 334.1 (M^+) Exact mass calcd for $C_{18}H_{14}N_4OS$: m/z 334.0888; found 334.0877. Yield: 99%.

3-5d: 1,7-Dibenzyl-2-thioxanthine. ^{1}H NMR (DMSO-d_6): δ 13.74 (s, *NH*, 1H), 8.34 (s, *CH*, 1H), 7.31-7.18 (m, *ArH*, 10H), 5.63 (s, N1*CH_2*, 2H), 5.48 (s, N7*CH_2*, 2H); ^{13}C NMR (DMSO-d_6): δ 174.7, 153.5, 147.9, 144.2, 136.8, 136.7, 128.7, 128.1, 127.9, 127.4, 127.0, 126.8, 109.2, 49.0, 48.5; Mass spectrum (EI) m/z 348.1 (M^+) Exact mass calcd for $C_{19}H_{16}N_4OS$: m/z 348.1045; found 348.1047. Yield: 99%.

3.4.5 Synthesis of 7-benzyl-2-methylthio-1-substituted-1*H*-purin-6(7*H*)-one (3-6)

A suspension of compound **3-5a** (0.3246 g, 1.13 mmol) in 10% KOH solution (10 mL) was cooled in an ice-water bath and CH_3I (0.14 mL, 2.27 mmol) was added dropwise. The mixture was stirred at rt for 30 min. and the white precipitate which formed was filtered, washed with water and dried to give 7-benzyl-1-ethyl-2-methylthio-1*H*-purin-6(7*H*)-one (**3-6a**) as a white solid (0.56 g, 99% yield). ^{1}H NMR ($CDCl_3$): δ 7.75 (s, *CH*, 1H), 7.18-7.13 (m, *ArH*, 5H), 5.43 (s, Ar*CH*$_2$, 2H), 4.08-4.01 (q, *J* = 7.1 Hz, *CH*$_2$CH$_3$, 2H), 2.51 (s, S*CH*$_3$, 3H), 1.24-1.19 (t, *J* = 7.1 Hz, CH$_2$*CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 157.0, 155.8, 154.3, 142.5, 135.6, 128.5, 127.9, 127.5, 111.5, 49.8, 38.9, 14.9, 12.8; Mass spectrum (EI) m/z 300.1 (M^+) Exact mass calcd for $C_{15}H_{16}N_4OS$: m/z 300.1045; found 300.1045.

3-6b: 7-Benzyl-2-methylthio-1-propyl-1*H*-purin-6(7*H*)-one. ^{1}H NMR ($CDCl_3$): δ 7.75 (s, *CH*, 1H), 7.15-7.08 (m, *ArH*, 5H), 5.41 (s, Ar*CH*$_2$, 2H), 3.94-3.88 (t, *J* = 7.8 Hz, *CH*$_2$CH$_2$CH$_3$, 2H), 2.49 (s, S*CH*$_3$, 3H), 1.70-1.57 (m, CH$_2$*CH*$_2$CH$_3$, 2H), 0.87-0.82 (t, *J* = 7.5 Hz, CH$_2$CH$_2$*CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 157.0, 155.7, 154.3, 142.5, 135.6, 128.3, 127.7, 127.3, 111.3, 49.7, 45.1, 20.9, 14.9, 10.7; Mass spectrum (EI) m/z 314.0 (M^+) Exact mass calcd for $C_{16}H_{18}N_4OS$: m/z 314.1201; found 314.1200. Yield: 99%.

3-6c: 7-Benzyl-2-methylthio-1-phenyl-1*H*-purin-6(7*H*)-one. ^{1}H NMR ($CDCl_3$): δ 7.78 (s, *CH*, 1H), 7.41-7.17 (m, *ArH*, 10H), 5.39 (s, Ar*CH*$_2$, 2H), 2.39 (s, S*CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 158.8, 156.5, 154.8, 142.7, 135.4, 135.3, 129.7, 129.4, 129.0 128.7, 128.1, 127.8, 111.7, 50.1, 15.7; Mass spectrum (EI) m/z 348.0 (M^+) Exact mass calcd for $C_{19}H_{16}N_4OS$: m/z 348.1045; found 348.1044. Yield: 99%.

3-6d: 1,7-Dibenzyl-2-methylthio-1*H*-purin-6(7*H*)-one. ^{1}H NMR ($CDCl_3$): δ 7.82 (s, *CH*,

1H), 7.25-7.18 (m, *ArH*, 10H), 5.49 (s, N1*CH*$_2$, 2H), 5.31 (s, N7*CH*$_2$, 2H), 2.53 (s, S*CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 157.8, 156.0, 154.7, 142.8, 135.5, 135.0, 128.5, 128.1, 127.9, 127.5, 127.2, 126.8, 111.4, 49.9, 46.4, 15.2; Mass spectrum (EI) m/z 362.1 (M^+) Exact mass calcd for $C_{20}H_{18}N_4OS$: m/z 362.1201; found 362.1207. Yield: 99%.

3.4.6 Synthesis of 7-benzyl-2-methylsulfonyl-1-substituted-1*H*-purin-6(7*H*)-one (3-7)

To compound **3-6a** (0.2996 g, 0.998 mmol) in CH_2Cl_2 (10 mL) was added a solution of *m*-CPBA (70% purity, 0.5 g, 1.995 mmol) in CH_2Cl_2 (10 mL) dropwise in an ice-water bath. After that, the mixture was stirred at rt for 3 h, concentrated and purified by CC (EtOAc:hexane = 2:1) to give 7-benzyl-1-ethyl-2-methylsulfonyl-1*H*-purin-6(7*H*)-one (**3-7a**) as a white solid (0.315 g, 95% yield). ^{1}H NMR ($CDCl_3$): δ 7.93 (s, *CH*, 1H), 7.27-7.22 (m, *ArH*, 5H), 5.50 (s, Ar*CH*$_2$, 2H), 4.45-4.38 (q, *J* = 7.0 Hz, *CH*$_2$CH$_3$, 2H), 3.41 (s, SO$_2$*CH*$_3$, 3H), 1.34-1.30 (t, *J* = 7.0 Hz, CH$_2$*CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 153.5, 152.6, 151.8, 144.1, 134.9, 128.9, 128.5, 127.8, 115.5, 50.4, 41.3, 39.7, 13.9; Mass spectrum (EI) m/z 331.9 (M^+) Exact mass calcd for $C_{15}H_{16}N_4O_3S$: m/z 332.0943; found 332.0943.

3-7b: 7-Benzyl-2-methylsulfonyl-1-propyl-1*H*-purin-6(7*H*)-one. ^{1}H NMR ($CDCl_3$): δ 7.94 (s, *CH*, 1H), 7.25-7.20 (m, *ArH*, 5H), 5.48 (s, Ar*CH*$_2$, 2H), 4.28-4.23 (t, *J* = 8.0 Hz, *CH*$_2$CH$_2$CH$_3$, 2H), 3.39 (s, SO$_2$*CH*$_3$, 3H), 1.79-1.67 (m, CH$_2$*CH*$_2$CH$_3$, 2H), 0.89-0.85 (t, *J* = 7.3 Hz, CH$_2$CH$_2$*CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 153.5, 152.5, 151.7, 144.1, 134.9, 128.8, 128.4, 127.6, 115.3, 50.3, 45.5, 41.3, 22.0, 10.7; Mass spectrum (EI) m/z 346.1 (M^+) Exact mass calcd for $C_{16}H_{18}N_4O_3S$: m/z 346.1100; found 346.1103. Yield: 93%.

3-7c: 7-Benzyl-2-methylsulfonyl-1-phenyl-1*H*-purin-6(7*H*)-one. ^{1}H NMR ($CDCl_3$): δ 7.91 (s, *CH*, 1H), 7.43-7.22 (m, *ArH*, 10H), 5.42 (s, Ar*CH*$_2$, 2H), 3.29 (s, SO$_2$*CH*$_3$, 3H); ^{13}C NMR

($CDCl_3$): δ 154.1, 153.2, 151.7, 144.4, 134.8, 132.2, 130.2, 129.7, 129.0, 128.7, 128.6, 128.0, 115.5, 50.5, 41.4; Mass spectrum (EI) m/z 380.2 (M^+) Exact mass calcd for $C_{19}H_{16}N_4O_3S$: m/z 380.0943; found 380.0942. Yield: 90%.

3-7d: 1,7-Dibenzyl-2-methylsulfonyl-1*H*-purin-6(7*H*)-one. ^{1}H NMR ($CDCl_3$): δ 7.84 (s, *CH*, 1H), 7.19-7.10 (m, *ArH*, 10H), 5.58 (s, N1*CH*$_2$, 2H), 5.38 (s, N7*CH*$_2$, 2H), 3.40 (s, SO_2CH_3, 3H); ^{13}C NMR ($CDCl_3$): δ 153.6, 152.7, 152.0, 144.3, 135.1, 134.8, 128.9, 128.5, 128.2, 127.9, 127.4, 127.0, 115.6, 50.5, 47.1, 41.4; Mass spectrum (EI) m/z 394.1 (M^+) Exact mass calcd for $C_{20}H_{18}N_4O_3S$: m/z 394.1100; found 394.1100. Yield: 95%.

3.4.7 Synthesis of 7-benzyl-2-hydroxyalkylamino-1-substituted-1*H*-purin-6(7*H*)-one (3-8)

To compound **3-7b** (0.0335 g, 0.097 mmol) in ethanolamine (1 mL) was added molecular sieves (0.5 g) and the mixture was heated at 130 ºC for 30 min. After which, it was concentrated and purified by CC (EtOAc, then MeOH:CH_2Cl_2 = 1:5) to give 7-benzyl-2-(2-hydroxyethyl)amino-1-propyl-1*H*-purin-6(7*H*)-one (**3-8a**) as a colorless oil (0.0267 g, 84% yield). ^{1}H NMR (CD_3OD): δ 8.19 (s, *CH*, 1H), 7.37-7.28 (m, *ArH*, 5H), 5.54 (s, Ar*CH*$_2$, 2H), 4.01-3.96 (t, *J* = 7.8 Hz, *CH*$_2$CH$_2$CH$_3$, 2H), 3.77-3.73 (m, NCH$_2$*CH*$_2$OH, 2H), 3.60-3.57 (t, *J* = 5.6 Hz, N*CH*$_2$CH$_2$OH, 2H), 1.75-1.62 (m, CH$_2$*CH*$_2$CH$_3$, 2H), 0.99-0.94 (t, *J* = 7.5 Hz, CH$_2$CH$_2$*CH*$_3$, 3H); ^{13}C NMR (CD_3OD): δ 157.1, 156.3, 154.0, 143.2, 137.8, 129.9, 129.3, 128.9, 108.8, 61.5, 51.4, 45.5, 43.2, 21.7, 11.2; Mass spectrum (EI) m/z 327.2 (M^+) Exact mass calcd for $C_{17}H_{21}N_5O_2$: m/z 327.1695; found 327.1691.

3-8b: 7-Benzyl-2-(3-hydroxypropyl)amino-1-propyl-1*H*-purin-6(7*H*)-one. ^{1}H NMR (CD_3OD): δ 7.97 (s, *CH*, 1H), 7.32-7.26 (m, *ArH*, 5H), 5.50 (s, Ar*CH*$_2$, 2H), 3.98-3.92 (t, *J* =

7.7 Hz, $CH_2CH_2CH_3$, 2H), 3.68-3.64 (m, $NCH_2CH_2CH_2OH$, 2H), 3.59-3.54 (t, *J* = 6.6 Hz, $NCH_2CH_2CH_2OH$, 2H), 1.93-1.82 (m, $NCH_2CH_2CH_2OH$, 2H), 1.73-1.60 (m, $CH_2CH_2CH_3$, 2H), 0.98-0.93 (t, *J* = 7.3 Hz, $CH_2CH_2CH_3$, 3H); ^{13}C NMR (CD_3OD): δ 158.9, 156.6, 153.4, 144.5, 138.4, 129.1, 128.7, 108.9, 61.0, 50.9, 43.0, 40.7, 32.8, 21.8, 11.2; Mass spectrum (EI) m/z 341.1 (M^+) Exact mass calcd for $C_{18}H_{23}N_5O_2$: m/z 341.1852; found 341.1846. Yield: 78%.

3-8c: 7-Benzyl-2-(4-hydroxybutyl)amino-1-propyl-1*H*-purin-6(7*H*)-one. ^{1}H NMR ($CDCl_3$): δ 7.75 (s, *CH*, 1H), 7.44-7.30 (m, *ArH*, 5H), 5.49 (s, $ArCH_2$, 2H), 3.97-3.54 (m, $CH_2CH_2CH_3$ and $NCH_2CH_2CH_2CH_2OH$, 6H), 1.79-1.62 (m, $CH_2CH_2CH_3$ and $NCH_2CH_2CH_2CH_2OH$, 6H), 0.98-0.94 (t, *J* = 6.3 Hz, $CH_2CH_2CH_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 156.7, 155.0, 151.6, 141.9, 135.9, 128.9, 128.3, 127.9, 108.2, 62.1, 50.3, 42.1, 37.9, 29.6, 25.8, 20.9, 11.2; Mass spectrum (EI) m/z 341.1 (M^+) Exact mass calcd for $C_{18}H_{23}N_5O_2$: m/z 341.1852; found 341.1846. Yield: 70%.

3.4.8 Synthesis of polycyclic guanines (3-9)

To compound **3-8a** (0.0397 g, 0.121 mmol) and TEA (0.051 mL, 0.363 mmol) in CH_2Cl_2 (2 mL) was added a solution of $SOCl_2$ (0.045 mL, 0.605 mmol) in CH_2Cl_2 (1 mL) dropwise in an ice-water bath. After that, the mixture was stirred in the ice-water bath for an additional 30 min and then at rt for 1 h. The reaction mixture was then refluxed at 50-60 ºC for another 1 h then quenched with 10% KOH solution (1 mL), diluted with water (10 mL) and extracted with CH_2Cl_2 (20 mL x 3). The combined organic layer was dried with $MgSO_4$, filtered, concentrated and purified by CC (EtOAc, then MeOH:CH_2Cl_2 = 1:5) to give 3-benzyl-5-propyl-7,8-dihydro-3*H*-imidazo [2,1-*b*]purin-4(5*H*)-one (**3-9a**) as a colorless oil

(0.033 g, 90% yield). ^{1}H NMR (CD_3OD): δ 8.00 (s, *CH*, 1H), 7.35-7.29 (m, *ArH*, 5H), 5.50 (s, ArCH_2, 2H), 4.22-4.16 (t, *J* = 9.2 Hz, $CH_2CH_2CH_3$, 2H), 4.01-3.95 (t, *J* = 9.1 Hz, N6CH_2CH_2N, 2H), 3.88-3.83 (t, *J* = 7.7 Hz, N6CH_2CH_2N, 2H), 1.74-1.61 (m, $CH_2CH_2CH_3$, 2H), 0.97-0.92 (t, *J* = 7.5 Hz, $CH_2CH_2CH_3$, 3H); ^{13}C NMR (CD_3OD): δ 155.7, 155.5, 149.1, 143.7, 137.6, 129.9, 129.4, 128.9, 106.6, 50.9, 50.1, 46.9, 45.1, 21.4, 11.2; Mass spectrum (EI) m/z 309.0 (M^+) Exact mass calcd for $C_{17}H_{19}N_5O$: m/z 309.1590; found 309.1587.

3-9b: 3-Benzyl-5-propyl-8,9-dihydropyrimido[2,1-*b*]purin-4(5*H*)-one. ^{1}H NMR (CD_3OD): δ 8.03 (s, *CH*, 1H), 7.37-7.27 (m, *ArH*, 5H), 5.52 (s, ArCH_2, 2H), 4.12-4.10 (t, *J* = 5.7 Hz, N6$CH_2CH_2CH_2$N, 2H), 3.95-3.92 (t, *J* = 7.9 Hz, $CH_2CH_2CH_3$, 2H), 3.59-3.56 (t, *J* = 5.7 Hz, N6$CH_2CH_2CH_2$N, 2H), 2.08-2.05 (m, N6$CH_2CH_2CH_2$N, 2H), 1.67-1.59 (m, $CH_2CH_2CH_3$, 2H), 0.96-0.93 (t, *J* = 7.3 Hz, $CH_2CH_2CH_3$, 3H); ^{13}C NMR (CD_3OD): δ 155.2, 149.6, 147.4, 143.5, 137.7, 129.9, 129.4, 128.9, 107.3, 51.1, 44.0, 43.6, 43.1, 21.2, 20.0, 11.3; Mass spectrum (EI) m/z 323.0 (M^+) Exact mass calcd for $C_{18}H_{21}N_5O$: m/z 323.1746; found 323.1736. Yield: 89%.

3-9c: 3-Benzyl-5-propyl-7,8,9,10-tetrahydro-3*H*-[1,3]diazepino[2,1-*b*]purin-4(5*H*)-one. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.81 (s, *CH*, 1H), 7.34-7.27 (m, *ArH*, 5H), 5.50 (s, ArCH_2, 2H), 3.98-3.95 (t, *J* = 7.6 Hz, $CH_2CH_2CH_3$, 2H), 3.57-3.52 (m, N6$CH_2CH_2CH_2CH_2$N, 4H), 1.85-1.66 (m, $CH_2CH_2CH_3$ and N6$CH_2CH_2CH_2CH_2$N, 6H) 1.00-0.97 (t, *J* = 7.3 Hz, $CH_2CH_2CH_3$, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 156.2, 154.9, 151.4, 141.6, 135.7, 129.0, 128.4, 127.9, 108.3, 50.4, 44.8, 42.2, 41.6, 29.9, 26.5, 20.9, 11.3; Mass spectrum (EI) m/z 337.1 (M^+) Exact mass calcd for $C_{19}H_{23}N_5O$: m/z 337.1903; found 337.1899. Yield: 95%.

3-9d: 3-Benzyl-5-ethyl-8,9-dihydropyrimido[2,1-*b*]purin-4(5*H*)-one. ^{1}H NMR (CD_3OD,

500 MHz): δ 7.97 (s, *CH*, 1H), 7.37-7.29 (m, *ArH*, 5H), 5.50 (s, Ar*CH*$_2$, 2H), 4.06-4.00 (m, *CH*$_2$CH$_3$ and N6CH$_2$CH$_2$*CH*$_2$N, 4H), 3.56-3.54 (t, *J* = 5.7 Hz, N6*CH*$_2$CH$_2$CH$_2$N, 2H), 2.03-1.98 (m, N6CH$_2$*CH*$_2$CH$_2$N, 2H), 1.19-1.16 (t, *J* = 7.0 Hz, CH$_2$*CH*$_3$, 3H); ^{13}C NMR (CD$_3$OD, 126 MHz): δ 155.5, 149.9, 146.6, 143.1, 137.7, 129.9, 129.3, 128.9, 106.8, 51.0, 43.8, 43.7, 37.2, 20.4, 12.7; Mass spectrum (EI) m/z 309.0 (M^+) Exact mass calcd for $C_{17}H_{19}N_5O$: m/z 309.1590; found 309.1588. Yield: 94%.

3-9e: 3-Benzyl-5-phenyl-7,8-dihydro-3*H*-imidazo[2,1-*b*]purin-4(5*H*)-one. ^{1}H NMR (CD$_3$OD): δ 8.01 (s, *CH*, 1H), 7.53-7.28 (m, *ArH*, 10H), 5.44 (s, Ar*CH*$_2$, 2H), 4.17-4.11 (t, *J* = 9.2 Hz, N6CH$_2$*CH*$_2$N, 2H), 3.56-3.54 (t, *J* = 9.2 Hz, N6*CH*$_2$CH$_2$N, 2H); ^{13}C NMR (CD$_3$OD): δ 156.4, 156.4, 150.2, 143.7, 137.6, 136.9, 130.6, 130.1, 130.1, 129.9, 129.4, 129.0, 106.3, 51.5, 50.9, 47.1; Mass spectrum (EI) m/z 343.0 (M^+) Exact mass calcd for $C_{20}H_{17}N_5O$: m/z 343.1433; found 343.1418. Yield: 89%.

3-9f: 3,5-Dibenzyl-7,8-dihydro-3*H*-imidazo[2,1-*b*]purin-4(5*H*)-one. ^{1}H NMR (CD$_3$OD, 500 MHz): δ 7.93 (s, *CH*, 1H), 7.36-7.19 (m, *ArH*, 10H), 5.44 (s, N3*CH*$_2$, 2H), 5.08 (s, N5*CH*$_2$, 2H), 4.11-4.08 (t, *J* = 9.1 Hz, N6CH$_2$*CH*$_2$N, 2H), 3.92-3.89 (t, *J* = 9.1 Hz, N6*CH*$_2$CH$_2$N, 2H); ^{13}C NMR (CD$_3$OD, 126 MHz): δ 156.3, 155.7, 149.8, 143.4, 138.0, 137.7, 129.9, 129.4, 128.9, 128.8, 128.4, 128.3, 105.9, 51.8, 50.9, 47.2, 46.2; Mass spectrum (EI) m/z 357.1 (M^+) Exact mass calcd for $C_{21}H_{19}N_5O$: m/z 357.1590; found 357.1560. Yield: 92%.

3.5 References

[1] Ashton, M. J.; Cook, D. C.; Fenton, G.; Karlesson, J. A.; Palfreyman, M. N.; Raeburn, D.; Ratcliffe, A. J.; Souness, J. E.; Thurairatnam, S.; Vicker, N. *J. Med. Chem.* **1994**, *37*, 1696-1703. (b) Raeburn, D.; Souness, J. E.; Tomkinson, A.; Karlsson, J. A. *Prog. Drug. Res*. **1993**, *40*, 9-32.

[2] Ahn, H.-S.; Bercovici, A.; Boykow, G.; Bronnenkant, A.; Chackalamannil, S.; Chow, J.; Cleven, R.; Cook, J.; Czarniecki, M.; Domalski, C.; Fawzi, A.; Green, M.; Gundes, A.; Ho, G.; Laudicina, M.; Lindo, N.; Ma, K.; Brian McKittrick, M.-M.; Mirzai, B.; Nechuta, T.; Neustadt, B.; Puchalski, C.; Pula, K.; Silverman, L.; Smith, E.; Stamford, A.; Tedesco, R. P.; Tsai, H.; Tulshian, D.; Vaccaro, H.; Watkins, R. W.; Weng, X.; Witkowski, J. T.; Xia, Y.; Zhang, H. *J. Med. Chem.* **1997**, *40*, 2196-2210. (b) Vemulapalli, S.; Watkins, R. W.; Chintala, M.; Davis, H.; Ahn, H.-S.; Fawi, A.; Tulshian, D.; Chiu, P.; Chatterjee, M.; Lin, C.-C.; Sybertz, E. J. *J. Cardiovasc. Pharmacol*. **1996**, 28, 862-869.

[3] Asberom, T.; Clader, J. W.; Hu, Y.; Pissarnitski, D. A.; Stamford, A. W.; Xu, R. WO2003042216, **2003**. (b) Neustadt, B. R.; Lindo, N. A.; McKittrick, B. A. U. S. Patent. 5393755, **1995**. (c) Tulshian, D.; Mckittrick, B. A.; Xia, Y.; Chackalamannil, S.; Gala, D.; Dibenedetto, D. J.; Kugelman, M. WO199419351, **1994**. (d) Pissarnitski, D. A.; Asberom, T.; Boyle, C. D.; Chackalamannil, S.; Chintala, M.; Clader, W. J.; Greenlee, W. J.; Hu, Y.; Kurowski, S.; Myers, J.; Palamanda, J.; Stamford, A. W.; Vemulapalli, S.; Wang, Y.; Wang, P.; Wu, P.; Xu, R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1291–1294. (e) Suzuki, H.; Yamamoto, M.; Shimura, S.; Miyamoto, K., M.;

Yamamoto, K.; Sawanishi, H. *Chem. Pharm. Bull.* **2002**, *50*, 1163-1168. (f) Gala, D.; DiBenedetto, D. J.; Gloor, G.; Jenkins, J.; Kugelman, M.; Maloney, D.; Miller, A. *Org. Process Res. Dev.* **2004**, *8*, 396-400. (g) Junichi, S.; Takeshi, K.; Fumio, S. *J. Heterocyclic Chem.* **1993**, 30, 241-246. (h) Gala, D.; DiBenedetto, D. J; Kugelman, M.; Mitchell, M. B. *Tetrahedron Lett.* **2003**, *44*, 2721-2723.

[4] He, R.; Lam, Y. *J. Comb. Chem.* **2005**, *7*, 916-920. (b) He, R.; Ching, S.-M.; Lam, Y. *J. Comb. Chem.* **2006**, *8*, 923-928.

[5] Tumelty, D.; Cao, K.; Holmes, C. P. *Org. Lett.* **2001**, *3*, 83-86. (b) Guiney, D.; Gibson, C. L.; Suckling, C. J. *Org. Biomol. Chem.* **2003**, *1*, 664-675. (c) Hirota, K.; Kazaoka, K.; Niimoto, I.; Sajiki, H. *Org. Biomol. Chem.* **2003**, *1*, 1354-1365. (d) Ivachtchenko, A. V.; Kovalenko, S. M.; Drushlyak, O. G.. *J. Comb. Chem.* **2003**, *5*, 775-788.

[6] Kang, Y.; Kim, S.; Myoung, Y.; Baek, D. *Heterocycles* **2000,** *53*, 1551-1557.

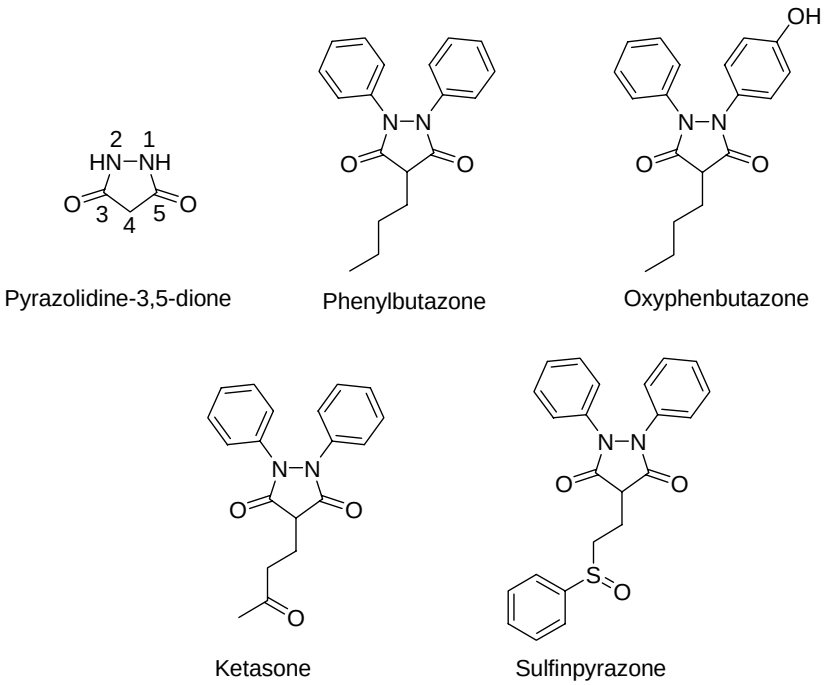
Chapter 4 Microwave-Assisted Combinatorial Solid-Phase Synthesis of Pyrazolidine-3,5-diones

4.1 Introduction

4.1.1 Importance of pyrazolidine-3,5-diones

Pyrazolidine-3,5-diones are well known for their anti-inflammatory properties because their pharmacologic spectrum is very similar to Aspirin.[1] Many derivatives have been clinically used for the treatment of various diseases. Phenylbutazone (brand name Butazolidine),[2] oxyphenbutazone (brand name Tandearil),[2c,3] ketasone,[4] sulfinpyrazone (brand name Anturane),[5] are very effective in treating fever, pain, inflammation, arthritis, bursitis; and as a uric acid lowering drug in the prevention and treatment of gout. Besides these, there are also many other derivatives of pyrazolidine-3,5-diones which have been used for other anti-inflammatory applications.[5b,6] More recently, this class of compounds was discovered to inhibit viral infections, especially those resulting in HIV/AIDS, and measles,[7] as the compounds are able to reduce metabolic activity in cells affected with HIV/AIDS, measles and other viral diseases, thereby reducing viral production and potentially killing the infected cell. Studies have also shown that antiviral pyrazolidine-3,5-diones possess a better inhibitory effects than AZT, which is known to block the replication of HIV.[8]

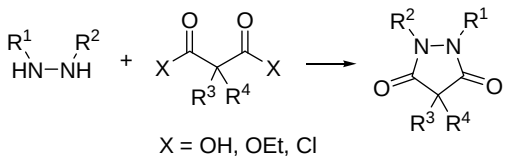
Figure 4-1 Structures of Some Pyrazolidine-3,5-dione Drugs



4.1.2 General methods for solution-phase synthesis of pyrazolidine-3,5-diones

Among the various methods for synthesizing pyrazolidine-3,5-diones, the classical and most popular one is through the condensation of hydrazines with malonic acids or their derivatives (Scheme 4-1).[5b,9] However the reaction conditions for these condensation are not mild - they either required long reaction times (up to a few days), high temperature (150 °C), or extremely expensive or uncommon reactants. A slightly different method was developed by Graziano Baccolini[10] who prepared *N*-alkenyl-pyrazolidine-3,5-diones from ketone hydrazones, $PC1_3$ and malonic acid.

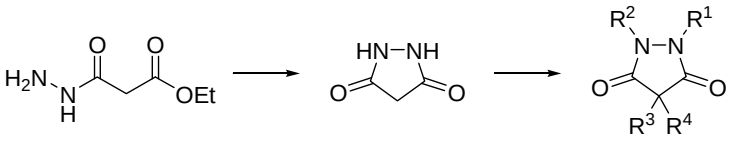
Scheme 4-1 Synthesis of Pyrazolidine-3,5-diones via Malonic Acid Derivatives



Using this synthetic route, non-substituted pyrazolidine-3,5-dione was prepared through the

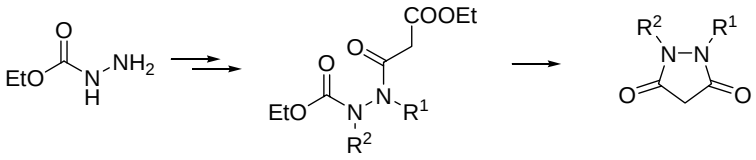
cyclization of ethyl malonyl hydrazide (Scheme 4-2). This non-substituted pyrazolidine-3,5-dione was subsequently alkylated to provide the substituted products.[11] Since all the 1, 2 and 4 positions of pyrazolidine-3,5-dione can be easily alkylated, it was difficult to realize the differences between R^1, R^2, R^3 and R^4, hence reducing the diversity of the final compounds.

Scheme 4-2 Synthesis of Pyrazolidine-3,5-diones via Ethyl Malonyl Hydrazide



To circumvent this problem, Lawton and coworkers have reported the synthesis of substituted pyrazolidine-3,5-diones through a stepwise *N*-alkylation prior to ring closure (Scheme 4-3).[12] In this method, although the whole synthesis was few steps longer than the methods mentioned earlier, common reagents and mild reaction conditions were used, and the yield for each step was often more than 90%. Furthermore alkylations of N1 and N2 were carried out in different steps, which thus allowed a variety of substitutents to be used.

Scheme 4-3 Synthesis of Pyrazolidine-3,5-diones via Ethyl Carbazate

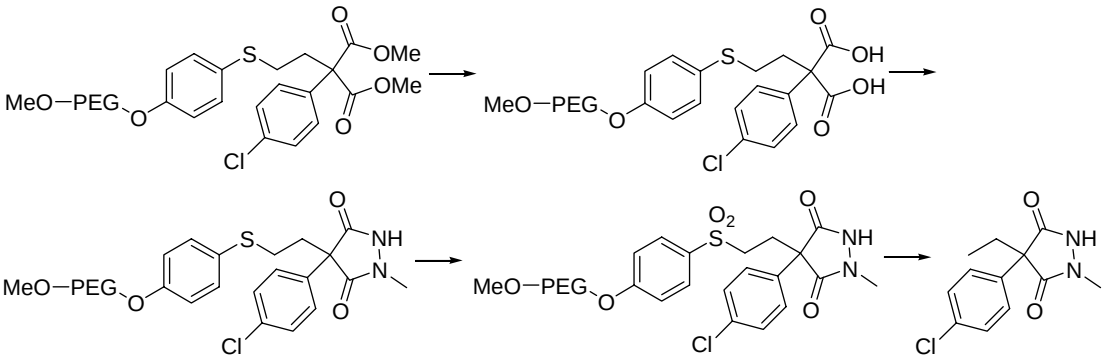


4.1.3 General methods for solid-phase synthesis of pyrazolidine-3,5-diones

To our knowledge, there is thus far only one report on the polymer-supported synthesis of pyrazolidine-3,5-diones.[14] In this paper (Scheme 4-4) liquid-phase approach using PEG as a polymeric support for the synthesis was described. Due to the nature and position of this support, the product released contained a remnant tether at the 4-position, which thus results

in the loss of one diversity point.

Scheme 4-4 Liquid-Phase Synthesis of Pyrazolidine-3,5-diones



4.1.4 Objectives and scope of this study

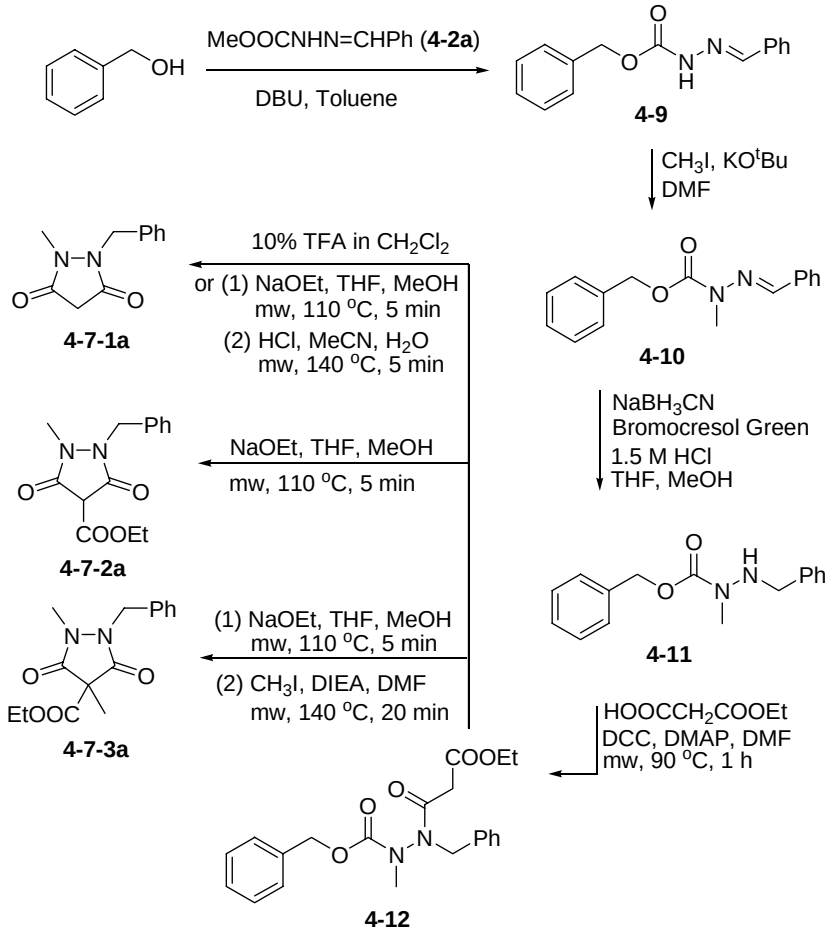
Since the solid-phase synthesis of pyrazolidine-3,5-diones has not been explored, we decided to embark on this project, which aims to develop a traceless solid-phase synthetic methodology to this class of compounds.

4.2 Results and Discussion

4.2.1 Solution-phase synthesis of pyrazolidine-3,5-diones

Prior to SPS, preliminary solution-phase studies (Scheme 4-5) were carried out to survey the required reaction conditions and establish the optimizations required for SPS.

Scheme 4-5 Microwave-Assisted Solution-Phase Synthesis of Pyrazolidine-3,5-diones



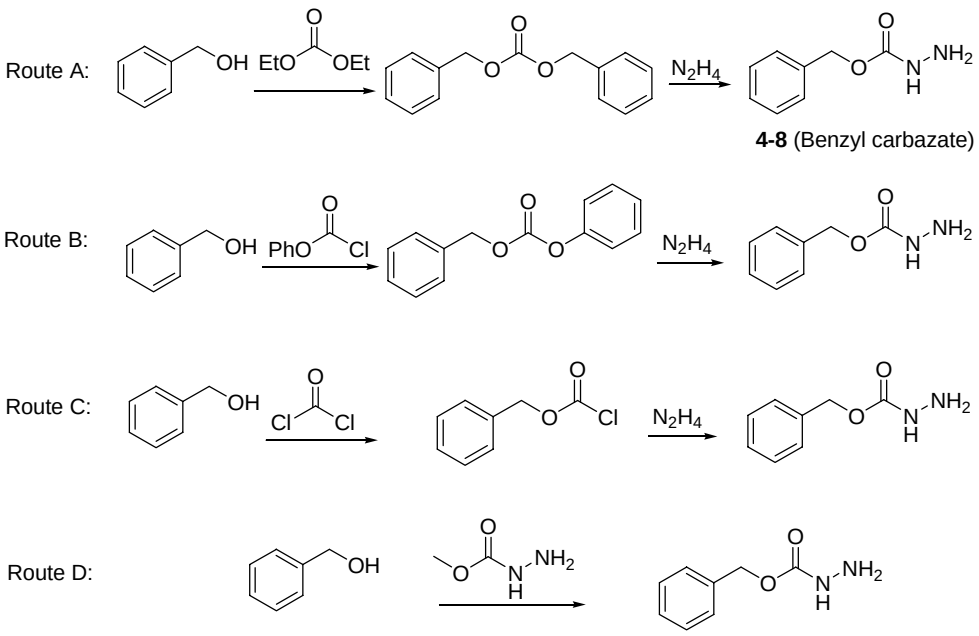
4.2.1.1 Synthesis of benzyl 3-benzylidenecarbazate (4-9)

In our initial synthetic strategy, we had intended to prepared benzyl carbazate from benzyl alcohol, the Wang resin mimic. Various existing routes to benzyl carbazate (**4-8**) (Scheme 4-6) were explored: Route A and route B could not be adapted for our solid-phase synthesis as they could result in a premature cleavage from the solid support. Synthesis of **4-8** via Route C

involved the preparation of an intermediate which was highly unstable and difficult to handle. Hence, we thought that Route D would probably be the best method to **4-8**. Unfortunately self-condensation of methyl carbazate occurred readily and the desired **4-8** was not observed. Although this problem could have been circumvented by protecting the primary amine of methyl carbazate, we perceived that a protection de-protection strategy would add two more steps to the solid-phase synthesis, thus making it less elegant. Considering that the next step was to convert the primary amine to an imine, we decided to synthesize the imine before attaching it to the polymeric support. By doing so, **4-9** could be prepared in a single step, instead of three steps, on solid-phase.

Methyl 3-benzylidenecarbazate (**4-2a**), which was prepared by reacting methyl carbazate (**4-1**) with benzyl aldehyde in MeOH, was treated with benzyl alcohol in the presence of DBU to give benzyl 3-benzylidenecarbazate (**4-9**) in 85% yield. The yield of this reaction was slightly lower than most typical ester exchange reactions because, in our reaction, benzyl alcohol had to be the limiting reactant and thus could not be used in large excess to drive the reaction to completion.

Scheme 4-6 Synthesis of Benzyl Carbazate



4.2.1.2 Synthesis of benzyl 3-benzylidene-2-methylcarbazate (4-10)

According to Lawton's procedure,[12] **4-9** could be converted to benzyl 3-benzylidene-2-methylcarbazate (**4-10**) by using K_2CO_3 as a base for the alkylation. However K_2CO_3 has poor solubility in the organic solvents, which provide good resin swelling. Hence we were required to search for an alternative base for our solid-phase reaction (Table 4-1). Despite using the strongest alkylating agent, CH_3I, all reactions carried out using amine bases failed. This may be attributed to the amines, which were too weakly basic to remove the proton on the nitrogen of **4-9**. Similar reactions carried out using inorganic salts such as KO^tBu and NaH worked very well. It is interesting to note that alkylation with CH_3I using KO^tBu as base gave a better yield than NaH, but alkylation with other alkylating agents, such as BnBr, PrBr and allyl bromide, gave better yields with NaH rather than with KO^tBu. These results could possibly be due to a combination of the alkylating ability of the reagents and the basicity of bases: CH_3I is the strongest alkylating

agent, and NaH is a stronger base than KO^{t}Bu. Thus a reaction involving CH_3I and NaH would be much harsher than if other combinations of alkylating agent and base were used and the reaction may give byproducts which results in a lower yield. By the same token, BnBr, PrBr and allyl bromide are weaker alkylating regents compared to CH_3I, and thus would require a stronger base, such as NaH, to give a higher yield. Based on our experimental results, two alkylation conditions (entries 8 and 11 in Table 4-1) were select for application on SPS.

Table 4-1 Synthesis of **4-10**

Entry	*Base*	*Alkylating agent*	*Solvent*	*Conditions*	*Result*
1	K_2CO_3	BnBr/$BrCH_2COOEt$	Acetone	reflux, 24 h	90% yield
2	TEA	CH_3I/BnBr/$BrCH_2COOEt$	CH_2Cl_2/THF	rt/reflux	No product
3	DIEA	CH_3I/BnBr/$BrCH_2COOEt$	CH_2Cl_2/THF	rt/reflux	No product
4	Urea	$BrCH_2COOEt$	Acetone	reflux	No product
5	TMG	$BrCH_2COOEt$	Acetone	reflux	No product
6	DBU	BnBr/$BrCH_2COOEt$	Acetone	reflux	Trace product
7	KO^{t}Bu	CH_3I	^{t}BuOH/THF	rt, 2 h	58% yield
8	KO^{t}Bu	CH_3I	THF/DMF	rt, 2 h	92% yield
9	KO^{t}Bu	BnBr/$BrCH_2COOEt$	THF/DMF	rt, 12 h	22-47% yield
10	NaH	CH_3I	THF/DMF	rt, 2 h	60% yield
11	NaH	BnBr/$BrCH_2COOEt$	DMF	rt, 12 h	86-76% yield

4.2.1.3 Synthesis of benzyl 3-benzyl-2-methylcarbazate (4-11)

We had earlier reported a modified methodology for imine reduction (using $NaBH(OAc)_3$ and HOAc in DMF (1%)).[13] However attempts to reduce **4-10** using this methodology failed to provide the desired **4-11**. Replacing $NaBH(OAc)_3$ with a stronger reducing agent such as $NaBH_4$ in MeOH, THF or DMF and in the presence or absence of an acid catalyst also failed

to provide the desired compound. Using H_2 with palladium-charcoal was not considered because of the insolubility of the catalyst, which can not be used in solid-phase reactions. Finally we tried $NaBH_3CN$ with dilute HCl,[12] which gave **4-11** in 95% yield.

4.2.1.4 Synthesis of benzyl 3-benzyl-3-ethoxycarbonylacetyl-2-methylcarbazate (4-12)

It was reported earlier[12] that acylation of **4-11** with ethoxycarbonylacetyl chloride and TEA in benzene gave 3-benzyl-3-ethoxycarbonylacetyl-2-methylcarbazate (**4-12**) in 84% yield. Unfortunately, in our hands, we were unable to reproduce this result. Attempts to vary the reaction conditions (Table 4-2) failed to improve the reaction. An alternative was to conduct a coupling reaction using ethyl hydrogen malonate and different coupling reagents in DMF. DCC and a catalytic amount DMAP gave the product **4-12** in 66% yield, but there was always some starting material **4-11** leftover, even after increasing the quantities of ethyl hydrogen malonate and DCC, prolonging the reaction or heating. Using stronger coupling reagents such as BOP, HATU also proved to be ineffective in improving the yield. Eventually, we sought to carry out the reaction under microwave conditions. To our delight, the reaction worked remarkably well under microwave irradiation and **4-12** was obtained in 93% yield. Optimization of the microwave reaction indicated that the best reaction condition was at 90 °C for 1 h.

Table 4-2 Synthesis of **4-12**

Entry	*Base*	*Reagent*	*Solvent*	*Conditions*	*Result*
1	/	EtO_2CCH_2COCl	THF	0 °C, rt, reflux	No product
1	TEA	EtO_2CCH_2COCl	CH_2Cl_2/$CHCl_3$/ Acetone/THF/ Toluene/Benzene	0 °C, rt, reflux	No product
2	DIEA	EtO_2CCH_2COCl	CH_2Cl_2/THF	rt/reflux	No product
3	DBU	EtO_2CCH_2COCl	CH_2Cl_2/THF	rt/reflux	No product
4	KO^tBu	EtO_2CCH_2COCl	^{t}BuOH, THF	rt	46% yield
5	KO^tBu	EtO_2CCH_2COCl	THF	rt	43% yield
6	KO^tBu	EtO_2CCH_2COCl	DMSO	rt	No product
7	NaH	EtO_2CCH_2COCl	DMF	rt	No product
8	BuLi	EtO_2CCH_2COCl	THF	-76, 0 °C, rt	No product
9	/	EtO_2CCH_2COOH DMAP, DCC	DMF	rt, 12 h	68% yield
10	/	EtO_2CCH_2COOH DMAP, DCC	DMF	rt, 48 h	68% yield
11	DIEA	EtO_2CCH_2COOH EDC	DMF	rt, 12 h	40% yield
12	DIEA	EtO_2CCH_2COOH DMAP, EDC	DMF	rt, 12 h	53% yield
13	DIEA	EtO_2CCH_2COOH BOP	DMF	rt, 24 h	Trace product
14	Collidine	EtO_2CCH_2COOH HATU	DMF	rt, 24 h	Trace product
15	/	EtO_2CCH_2COOH DMAP, DCC	DMF	mw, 60 °C 1 h	90% yield
16	/	EtO_2CCH_2COOH DMAP, DCC	DMF	mw, 90 °C 1 h	93% yield
17	/	EtO_2CCH_2COOH DMAP, DCC	DMF	mw, 120 °C 1 h	85% yield

4.2.1.5 Synthesis of 1-benzyl-4-ethoxycarbonyl-2-methylpyrazolidine-3,5-dione (4-7-2a)

Subsequently, **4-12** was cyclized with NaOEt in MeOH and THF to give **4-7-2a** in quantitative yield. Under microwave irradiation, the reaction was completed within 5 min

whilst conventional heating required 0.5 h.

4.2.1.6 Synthesis of 1-benzyl-2-methylpyrazolidine-3,5-dione (4-7-1a)

Compound **4-7-2a** was decarboxylated using H_2O and MeCN in the presence of catalytic amounts of dilute HCl to afford **4-7-1a**. Under conventional heating, the decarboxylation reaction was complete in 3 h, whereas for microwave-assisted reactions needed only 5 min to complete. It is worth noting that **4-7-1a** could also be obtained directly from **4-12** by treatment with TFA in CH_2Cl_2. Although the yields are generally good, but compared to the two-step cyclization-decarboxylation reaction, the overall yield for the two step reaction is higher than the one-pot transformation.

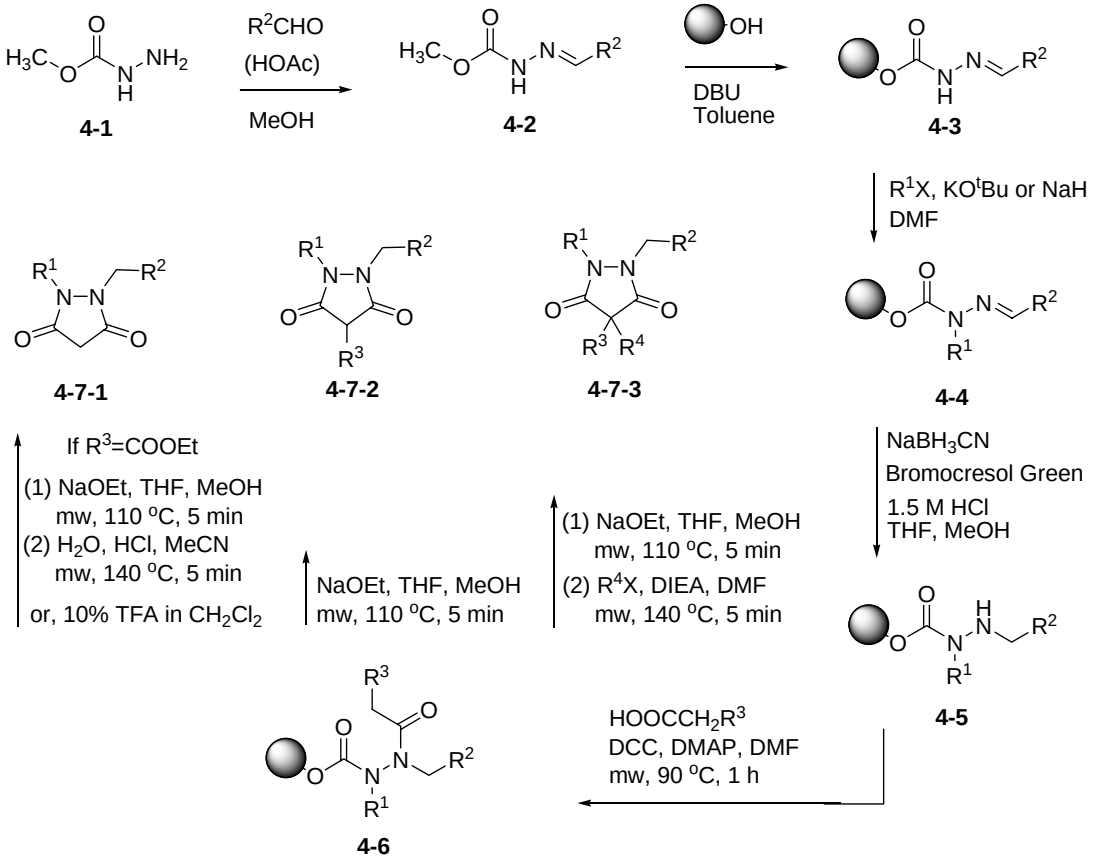
4.2.1.7 Synthesis of 1-benzyl-2,4-dimethyl-4-ethoxycarbonylpyrazolidine-3,5-dione (4-7-3a)

To obtain 4-substituted-4-ethoxycarbonyl pyrazolidine-3,5-dione, **4-7-2a** was alkylated with CH_3I in the presence of a base. Various bases were tested and DIEA proved to be better than TEA, DBU, Li_2CO_3, and NaOEt. In addition, the reaction time could be significantly reduced from 16 h to 20 min by microwave irradiation.

4.2.2 Solid-phase synthesis of pyrazolidine-3,5-diones

With the solution-phase pathway established, we proceeded to prove the versatility of this methodology for SPS (Scheme 4-7).

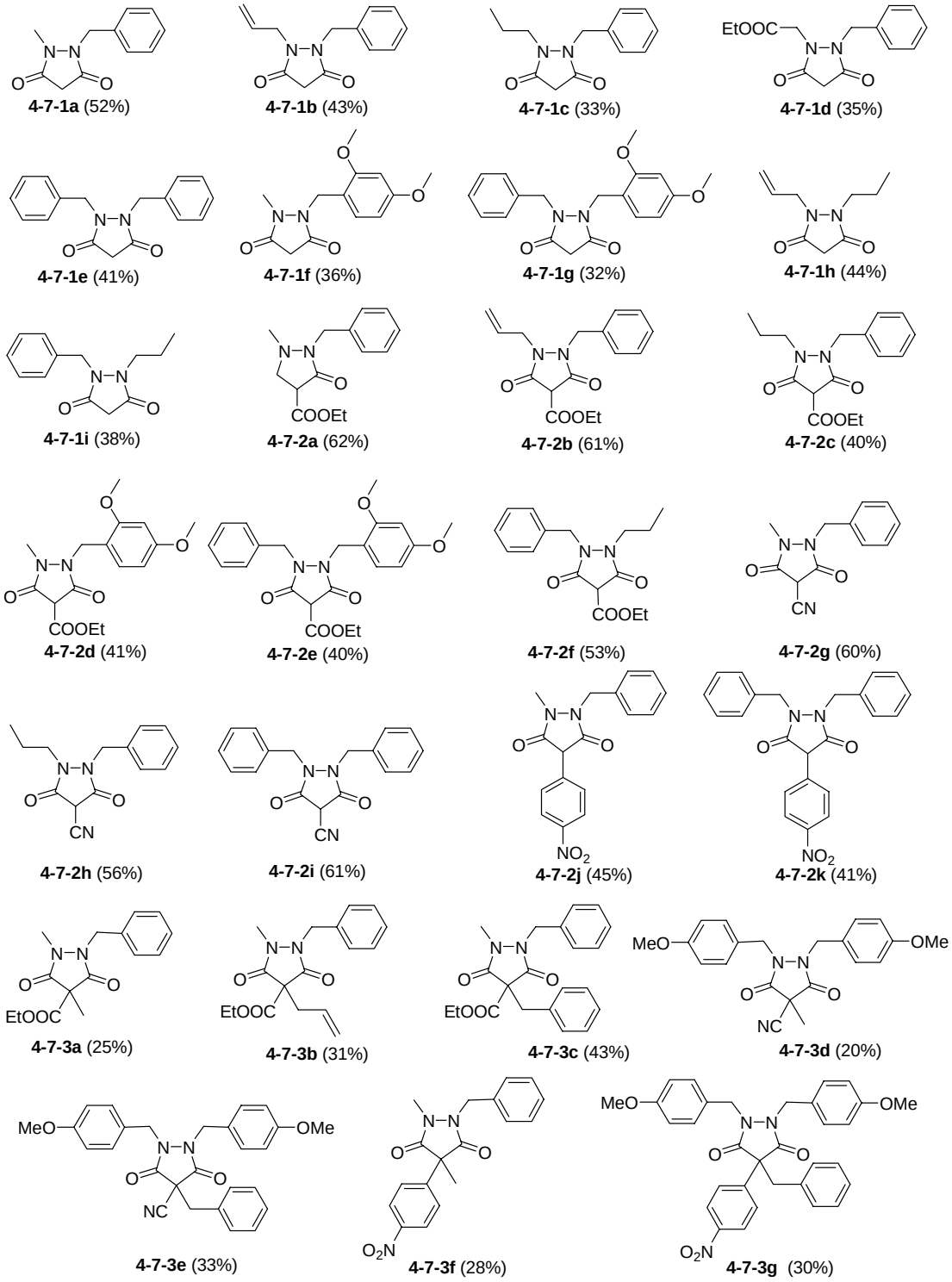
Scheme 4-7 Microwave-Assisted SPS of Pyrazolidine-3,5-diones



Methyl carbazate (**4-1**) was reacted with an equal molar of the respective aldehyde in MeOH to give **4-2**. The crude **4-2** obtained was subsequently treated with Wang resin by an ester exchange reaction to give **4-3** (Scheme 4-7). This reaction was amenable to KBr FTIR monitoring (disappearance of the OH stretch at 3566.0 cm^{-1} and appearance of a strong ester peak at 1739.6 cm^{-1}). Using the reaction conditions established in our solution-phase study (Table 4-1), resin **4-3** was alkylated with different alkylating agents to afford **4-4**. To ensure that the reaction proceeded to completion, resin **4-3** was stirred with KO^tBu or NaH in DMF for 1 h before the alkylating agent was added. Resin **4-4** was subsequently reduced with

$NaBH_3CN$ to afford resin **4-5**. Formation of resin **4-5** could be monitored using KBr FTIR by the appearance of an NH stretch at 3299.1 cm^{-1}. Using the acylation conditions established in our solution-phase study, we proceeded to acylate **4-5** by microwave irridiation. Ethyl hydrogen malonate, cynoacetic acid, 4-nitrophenyl acetic acid and diphenyl acetic acid were selected as examples for the acylation reaction. However only the first 3 acids were applicable because the product from diphenyl acetic acid could not be cyclized. With resin **4-6** in hand, we proceeded to synthesize various 1,2,4-trisubstituted pyrazolidine-3,5-diones (**4-7-2**) by treating the resin with NaOEt in EtOH and THF under microwave irradiation. A one-pot cyclization-alkylation could also be carried out by further treating the crude reaction mixture with various alkyl halides under microwave irradiation to afford compound **4-7-3**. Alternatively, the crude mixture could also be reacted with HCl in CH_3CN under microwave conditions to facilitate a one-pot decarboxylation to give 1,2-substituted pyrazolidine-3,5-diones (**4-7-1**). To illustrate the versatility of this chemistry, a representative set of 27 compounds, including 9 disubstituted, 11 trisubstituted and 7 tetrasubstituted pyrazolidine-3,5-diones was prepared (Figure 4-2). Only product **4-7-1d** could not be formed under base cleavage method and was prepared via an acid cleavage method. The overall yields obtained were 20-62%, indicating that the average yield for each step was greater than 85%.

Figure 4-2 Library of Substituted Pyrazolidine-3,5-diones **4-7**



4.3 Conclusion

This project investigated a solid-phase methodology for the preparation of pyrazolidine-3,5-diones. A preliminary solution-phase study was successfully carried out to

obtain the required reaction conditions, which were eventually adapted onto the solid-phase format. In this study, microwave irradiation was used in several steps of both the solid-phase and solution-phase syntheses to accelerate the reactions. These microwave-assisted reactions provided better yields than the traditional oil bath heating method. To the best of my knowledge, this is the first reported solid-phase synthesis of pyrazolidine-3,5-diones.

4.4 Experimental

Wang resin was purchased from Tianjin Nankai Hecheng Science and Technology Co (100-200 mesh, 1.4 mmol/g, 1% divinylbenzene cross-linking). All other chemical reagents were obtained from Aldrich, Merck, Lancaster or Fluka and used without further purification. The solid-phase rt reactions were agitated on a SF1 flask shaker (Stuart Scientific). Analytical TLC was carried out on pre-coated plates (Merck silica gel 60, F254) and visualized with UV light or stained with ninhydrin. CC was performed with silica (Merck, 70-230 mesh). ^{1}H NMR and ^{13}CNMR spectra were measured at 298 K on a Bruker DPX 300 or DPX 500 Fourier Transform spectrometer. Chemical shifts are reported in δ (ppm), relative to the internal standard of TMS. The signals observed are described as: s, d, t, q, m. The number of protons (n) for a given resonance is indicated as nH. All Infra-red spectra were recorded on a Bio-Rad FTS 165 spectrometer. Mass spectra were performed on VG Micromass 7035 spectrometer under EI, Finnigan/MAT LCQ under ESI (Normal), and Finnigan/MAT 95XL-T under ESI (Accurate).

4.4.1 Synthesis of benzyl 3-benzylidenecarbazate (4-9)

Benzyl alcohol (1.0000 g, 9.25 mmol), toluene (15 mL), methyl 3-benzylidenecarbazate (**4-2a**) (2.4720 g, 13.87 mmol) and DBU (0.4 mL, 2.775 mmol) were placed in a round bottom flask.

The mixture was refluxed for 3 h, then it was concentrated and purified by CC (EtOAc:hexane = 1:3) to give **4-9** as a white solid (2.000 g, 85% yield). ^{1}H NMR ($CDCl_3$): δ 8.67 (s, *NH*, 1H), 7.84 (s, *CH*, 1H), 7.67-7.33 (m, *ArH*, 10H), 5.25 (s, CH_2, 2H); ^{13}C NMR ($CDCl_3$): δ 153.7, 145.0, 135.8, 133.7, 129.9, 128.5, 128.3, 128.2, 127.5, 127.2, 126.9, 67.4; Mass spectrum (EI) m/z 254.0 (M^+) Exact mass calcd for $C_{15}H_{14}N_2O_2$: m/z 254.1055; found 254.1048.

4.4.2 Synthesis of benzyl 3-benzylidene-2-methylcarbazate (4-10)

Compound **4-9** (0.5000 g, 1.966 mmol) was dissolved in DMF (10 mL). KO^{t}Bu (0.4500 g, 3.933 mmol) was then added and the mixture was stirred at rt for 10 min. Subsequently it was cooled in an ice-water bath and CH_3I (0.4 mL, 5.9 mmol) was added dropwise. After that the mixture was stirred at rt for another 2 h, quenched with saturated NH_4Cl solution and extracted with ether (20 mL x 3). The combined organic layer was dried with $MgSO_4$, filtered, concentrated and purified by CC (EtOAc:hexane = 1:5). A colorless oil **4-10** was obtained (0.4858 g, 92% yield). ^{1}H NMR ($CDCl_3$): δ 7.76-7.34 (m, *ArH* and *CH*, 11H), 5.36 (s, CH_2, 2H), 3.38 (s, CH_3, 3H); ^{13}C NMR ($CDCl_3$): δ 154.3, 139.7, 136.1, 134.6, 129.3, 128.4, 128.2, 127.8, 127.7, 126.9, 67.8, 30.7; Mass spectrum (EI) m/z 267.9 (M^+) Exact mass calcd for $C_{16}H_{16}N_2O_2$: m/z 268.1212; found 268.1212.

4.4.3 Synthesis of benzyl 3-benzyl-2-methylcarbazate (4-11)

To compound **4-10** (0.2560 g, 0.954 mmol) in MeOH (5 mL) and THF (5 mL) was added $NaBH_3CN$ (0.1800 g, 2.86 mmol) and trace amounts of bromocresol green indicator. The resulting dark blue mixture was stirred at rt while 1.5 M HCl was added dropwise to just maintain the yellow color of the reaction mixture. When the yellow color persisted for 0.5 h

without further addition of acid, the mixture was concentrated and purified by CC (EtOAc:hexane = 1:5) to give **4-11** as a colorless oil (0.2448 g, 95% yield). ^{1}H NMR ($CDCl_3$): δ 7.47-7.30 (m, *ArH*, 10H), 5.22 (s, Ar*CH*$_2$OOC, 2H), 4.02 (s, Ar*CH*$_2$NH, 2H), 3.04 (s, *CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 156.5, 137.1, 136.2, 128.9, 128.2, 128.1, 127.8, 127.7, 127.2, 67.2, 53.8, 36.9; Mass spectrum (EI) m/z 270.1 (M^+) Exact mass calcd for $C_{16}H_{18}N_2O_2$: m/z 270.1368; found 270.1366.

4.4.4 Synthesis of benzyl 3-benzyl-3-ethoxycarbonylacetyl-2-methylcarbazate (4-12)

To compound **4-11** (0.230 g, 0.85 mmol) in DMF (5 mL) was added ethyl hydrogen malonate (0.30 mL, 2.55 mmol), DCC (0.530 g, 2,55 mmol) and DMAP (catalytic amount) in the stated order. The mixture was heated by microwave irradiation at 90 °C for 1 h, quenched with H_2O and extracted with ether (10 mL x 3). The combined organic layer was dried with $MgSO_4$, filtered, concentrated and purified by CC (EtOAc:hexane = 1:5, then 1:2) to provide **4-12** (0.305 g, 93% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.29-7.19 (m, *ArH*, 10H), 5.11-4.27 (m, Ar*CH*$_2$, 4H), 4.14-4.06 (q, *J* = 7.20 Hz, CH_3*CH*$_2$, 2H), 3.36-3.21 (m, *CH*$_2$, 2H), 2.80 (s, *CH*$_3$, 3H), 1.22-1.68 (t, *J* = 7.14 Hz, *CH*$_3$$CH_2$, 3H); ^{13}C NMR ($CDCl_3$): δ 168.4, 167.0, 155.2, 139.7, 135.3, 129.3, 128.7, 128.6, 128.5, 128.1, 128.0, 68.4, 61.4, 50.1, 40.2, 14.0; Mass spectrum (EI) m/z 383.9 (M^+) Exact mass calcd for $C_{21}H_{24}N_2O_5$: m/z 384.1685; found 384.1677.

4.4.5 Synthesis of 1-benzyl-4-ethoxycarbonyl-2-methylpyrazolidine-3,5-dione (4-7-2a)

To a solution of **4-12** (0.223 g, 0.58 mmol) in EtOH (5 mL) and THF (5 mL) was added NaOEt (21% (w/w) in denatured EtOH, 0.65 mL, 1.74 mmol). The mixture was heated by microwave irradiation at 110 °C for 5 min, then concentrated and purified by CC

(MeOH:CH_2Cl_2 = 1:5) to give **4-7-2a** (0.118 g, 99% yield) as a white solid. ^{1}H NMR (CD_3OD): δ 7.22 (s, *ArH*, 5H), 4.80 (s, Ar*CH*$_2$, 2H), 4.27-4.20 (q, *J* = 6.96 Hz, CH_3*CH*$_2$, 2H), 3.02 (s, *CH*$_3$, 3H), 1.29-1.25 (t, *J* = 6.98 Hz, *CH*$_3$$CH_2$, 3H); ^{13}C NMR ($CD_3OD$): δ 172.1, 170.7, 169.8, 137.9, 129.5, 129.0, 128.6, 82.5, 61.3, 47.8, 31.3, 14.9; Mass spectrum (EI) m/z 276.0 (M^+) Exact mass calcd for $C_{14}H_{16}N_2O_4$: m/z 276.1110; found 276.1112.

4.4.6 Synthesis of 1-benzyl-2-methylpyrazolidine-3,5-dione (4-7-1a)

Method A: To a solution of **4-12** (0.223 g, 0.58 mmol) in EtOH (5 mL) and THF (5 mL) was added NaOEt (21% (w/w) in denatured EtOH, 0.65 mL, 1.74 mmol). The mixture was heated by microwave irradiation at 110 °C for 5 min, then acidified, concentrated and dried in vacuum. To the resulting residue was added. 1.5 M HCl in MeCN (AR grade, 5 mL) and H_2O (5 mL). Then the mixture was heated under microwave irradiation at 140 °C for 5 min, concentrated and purified by CC (EtOAc:hexane = 1:1) to give product **4-7-1a** (0.1100 g, 93% yield) as a white solid.

Method B: To the stirring mixture of **4-12** (0.0228 g, 0.0593 mmol) in CH_2Cl_2 (5 mL) was added TFA (1 mL) dropwise. The reaction mixture was stirred at rt for 3 h then concentrated and purified by CC (EtOAc:hexane = 1:1) to give **4-7-1a** (0.087 g, 73% yield). ^{1}H NMR ($CDCl_3$): δ 7.30-7.19 (m, *ArH*, 5H), 4.78 (s, Ar*CH*$_2$, 2H), 3.17 (s, *CH*$_2$, 2H), 3.02 (s, *CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 167.0, 166.8, 134.8, 129.0, 128.4, 127.5, 46.9, 36.3, 30.5; Mass spectrum (EI) m/z 204.0 (M^+) Exact mass calcd for $C_{11}H_{12}N_2O_2$: m/z 204.0899; found 204.0902.

4.4.7 Synthesis of 1-benzyl-2,4-dimethyl-4-ethoxycarbonylpyrazolidine-3,5-dione (4-7-3a)

To a solution of **4-12** (0.223 g, 0.58 mmol) in EtOH (5 mL) and THF (5 mL) was added NaOEt (21% (w/w) in denatured EtOH, 0.65 mL, 1.74 mmol). The mixture was heated under microwave irradiation at 110 °C for 5 min, concentrated and dried in vacuum. The resulting residue was diluted with DMF (5 mL), and DIEA (0.60 mL, 3.48 mmol) and CH_3I (0.11 mL, 1.74 mmol) were added. The reaction mixture was heated under microwave irradiation at 140 °C for 20 min, concentrated and purified by CC (EtOAc:hexane = 1:3) to afford **4-7-3a** (0.076 g, 45% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.37-7.29 (m, *ArH*, 5H), 5.01-4.78 (m, Ar*CH*$_2$, 2H), 4.25-4.18 (q, *J* = 7.08 Hz, CH_3*CH*$_2$, 2H), 3.14 (s, N2*CH*$_3$, 3H), 1.60 (s, *CH*$_3$, 3H), 1.28-1.23 (t, *J* = 7.14 Hz, *CH*$_3$$CH_2$, 3H); ^{13}C NMR ($CDCl_3$): δ 168.1, 167.8, 164.9, 134.4, 129.0, 128.5, 127.6, 77.2, 62.8, 46.6, 30.7, 16.5, 13.9; Mass spectrum (EI) m/z 290.1 (M^+) Exact mass calcd for $C_{15}H_{18}N_2O_4$: m/z 290.1267; found 290.1267.

4.4.8 Preparation of methyl 3-alkylidenecarbazate (4-2)

To a solution of methyl carbazate (2.7 g, 30 mmol) in MeOH (AR grade, 30 mL) was added the respective aldehyde (30 mmol) and HOAc (glacial, 0.3 mL) (for benzaldehyde HOAc was unnecessary). The mixture was stirred at rt for 30 min and concentrated. The resulting white solid obtained was dried in a vacuum oven and used without further purification.

Methyl 3-benzylidenecarbazate (4-2a): ^{1}H NMR ($CDCl_3$): δ 8.54 (s, *NH*, 1H), 7.89 (s, *CH*, 1H), 7.67-7.35 (m, *ArH*, 5H), 3.80-3.76 (s, *CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 154.6, 144.9, 133.7, 129.9, 128.5, 127.2, 52.8; Mass spectrum (EI) m/z 177.9 (M^+) Exact mass calcd for $C_9H_{10}N_2O_2$: m/z 178.0742; found 178.0746.

Methyl 3-(2,4-dimethoxybenzylidene)carbazate (4-2b): ^{1}H NMR ($CDCl_3$): δ 8.55 (s, *NH*, 1H), 8.16 (s, *CH*, 1H), 7.87-6.36 (m, *ArH*, 3H), 3.80-3.76 (m, CH_3 and OCH_3, 9H); ^{13}C NMR ($CDCl_3$): δ 162.5, 159.0, 140.9, 127.8, 115.0, 105.4, 97.9, 55.4, 55.3, 52.7; Mass spectrum (EI) m/z 238.2 (M^+) Exact mass calcd for $C_{11}H_{14}N_2O_4$: m/z 238.0954; found 238.0952.

Methyl 3-propylidenecarbazate (4-2c): ^{1}H NMR ($CDCl_3$): δ 7.85 (s, *NH*, 1H), 7.16 (s, *CH*, 1H), 3.81 (s, CH_3, 3H), 2.37-2.28 (m, CH_2, 2H), 1.12-1.07 (t, *J* = 7.50 Hz, CH_3CH_2, 3H); ^{13}C NMR ($CDCl_3$): δ 154.6, 149.5, 52.8, 25.5, 10.9; Mass spectrum (EI) m/z 129.8 (M^+) Exact mass calcd for $C_5H_{10}N_2O_2$: m/z 130.0742; found 130.0741.

4.4.9 Preparation of benzyl 3-alkylidenecarbazate resin (4-3)

A mixture of Wang resin (5 g, 7 mmol), **4-2** (14 mmol), DBU (0.32 mL, 2.1 mmol) and toluene (40 mL) was refluxed for 24 h. The resin was then filtered, washed with DMF (20 mL x 3), H_2O (20 mL x 3), EtOH (20 mL x 3), CH_2Cl_2 (20 mL x 3), Et_2O (20 mL x 3) and dried overnight at 50 °C in a vacuum oven.

4.4.10 Preparation of benzyl 3-alkylidene-2-substitutedcarbazate resin (4-4)

A mixture of **4-3** (2 g, 2.213 mmol), KO^{t}Bu (0.4970 g, 4.426 mmol) [or NaH (60% dispersion in mineral oil, 0.177 g, 4.426 mmol)] and DMF (15 mL) was stirred at rt for 1 h. Subsequently the mixture was cooled in an ice-water bath and CH_3I (0.4 mL, 6.639 mmol) [or RX (other alkylating agents, 6.639 mmol)] was added dropwise. The mixture was then stirred at rt for another 12 h. The resin was then filtered, washed with DMF (20 mL x 3), H_2O (20 mL x 3), EtOH (20 mL x 3), CH_2Cl_2 (20 mL x 3), Et_2O (20 mL x 3) and dried overnight at 50 °C in a vacuum oven.

4.4.11 Preparation of benzyl 2,3-substitutedcarbazate resin (4-5)

To a suspension of **4-4** (2.0520 g, 2.213 mmol) in MeOH (8 mL) and THF (13 mL) was added $NaBH_3CN$ (0.4170 g, 6.639 mmol) and bromocresol green indicator (half spatula). 1.5 M HCl was then added dropwise to just maintain the yellow color of the solution. When the yellow color persisted for 1 h without further addition of acid, the resin was filtered, washed with DMF (20 mL x 3), H_2O (20 mL x 3), EtOH (20 mL x 3), CH_2Cl_2 (20 mL x 3), Et_2O (20 mL x 3) and dried overnight at 50 °C in a vacuum oven.

4.4.12 Preparation of benzyl 3-substitutedacetyl-2,3-substitutedcarbazate resin (4-6)

To **4-5** (1 g, 1.1 mmol) in DMF (10 mL) was added the respective substituted acetic acids (2.2 mmol), DCC (0.4540 g, 2.2 mmol) and DMAP (0.0400 g, 0.33 mol) in the stated order. The mixture was heated under microwave irradiation at 90 °C for 1 h then the resin was filtered, washed with DMF (20 mL x 3), H_2O (20 mL x 3), EtOH (20 mL x 3), CH_2Cl_2 (20 mL x 3), Et_2O (20 mL x 3) and dried overnight at 50 °C in a vacuum oven.

4.4.13 Preparation of 4-ethoxycarbonyl-1,2-substitutedpyrazolidine-3,5-dione (4-7-2)

A mixture of resin **4-6** (1.100 g, 1.1 mmol), NaOEt (21% (w/w) in denatured EtOH, 1.2 mL, 3.3 mmol), THF (6 mL) and EtOH (6 mL) was heated under microwave irradiation at 110 °C for 5 min. The resin was then filtered and washed with MeOH (10 mL x 3). The combined filtrate was concentrated and purified by CC (EtOAc:hexane = 1:1, MeOH:CH_2Cl_2 =1:5) to give product **4-7-2**.

4.4.14 Preparation of 4-cyano/(4-nitro)phenyl-1,2-substitutedpyrazolidine-3,5-dione (4-7-2)

A mixture of resin **4-6** (1.100 g, 1.1 mmol), NaOEt (21% (w/w) in denatured EtOH, 1.2 mL,

3.3 mmol), THF (6 mL) and EtOH (6 mL) was heated under microwave irradiation at 110 °C for 5 min. The resin was then filtered and washed with MeOH (10 mL x 3). The combined filtrate was concentrated, diluted with H_2O and, extracted with ether. The aqueous layer was acidified with 1.5 M HCl and the solid which precipitated was collected and washed with H_2O to give **7-2**. If no ppt formed, the acidified aqueous layer was extracted with CH_2Cl_2 and the CH_2Cl_2 extract obtained was dried with $MgSO_4$, filtered, concentrated to dryness to give product **4-7-2**.

4.4.15 Preparation of 1,2-substitutedpyrazolidine-3,5-dione (4-7-1) A mixture of resin **4-6** (1.100 g, 1.1 mmol), NaOEt (21% (w/w) in denatured EtOH, 1.2 mL, 3.3 mmol), THF (6 mL) and EtOH (6 mL) was heated under microwave irradiation at 110 °C for 5 min. After the mixture has cooled, it was acidified with 1.5 M HCl and concentrated. To the resulting solid was added MeCN (10 mL), H_2O (10 mL) and a few drops 1.5 M HCl. The mixture was heated under microwave irradiation at 140 °C for 5 min, filtered and washed with MeOH (10 mL x 3). The combined filtrate was concentrated and purified by CC (EtOAc:hexane = 1:1) to give product **4-7-1**. For compound **4-7-1d**, an acid cleavage method was used.

4.4.16 Preparation of 1,2,4,4-substitutedpyrazolidine-3,5-dione (4-7-3)

A mixture of resin **4-6** (1.100 g, 1.1 mmol), NaOEt (21% (w/w) in denatured EtOH, 1.2 mL, 3.3 mmol), THF (6 mL) and EtOH (6 mL) was heated under microwave irradiation at 110 °C for 5 min. After which, it was concentrated and dried. The resulting residue was diluted with DMF (10 mL), and DIEA (1.14 mL, 6.6 mmol) and CH_3I (0.21 mL, 3.3 mmol) were added. The reaction mixture was heated under microwave irradiation at 140 °C for 20 min, filtered and the resin was washed with MeOH (10 mL x 3). The combined filtrate was concentrated

and purified by CC (EtOAc:hexane = 1:3) to give product **4-7-3**.

4-7-1b: 2-Allyl-1-benzylpyrazolidine-3,5-dione. ^{1}H NMR ($CDCl_3$): δ 7.37-7.21 (m, *ArH*, 5H), 5.76-5.63 (m, CH_2CHCH_2N, 1H), 5.25-5.18 (m, CH_2CHCH_2N, 2H), 4.80 (s, $ArCH_2$, 2H), 4.11-4.09 (d, *J* = 5.55 Hz, CH_2CHCH_2N, 2H), 3.25 (s, CH_2, 2H); ^{13}C NMR ($CDCl_3$): δ 167.0, 166.9, 134.6, 130.9, 128.9, 128.3, 127.5, 119.4, 46.7, 45.6, 36.3; Mass spectrum (EI) m/z 229.8 (M^+) Exact mass calcd for $C_{13}H_{14}N_2O_2$: m/z 230.1055; found 230.1055.

4-7-1c: 1-Benzyl-2-propylpyrazolidine-3,5-dione. ^{1}H NMR ($CDCl_3$): δ 7.31-7.17 (m, *ArH*, 5H), 4.74 (s, $ArCH_2$, 2H), 3.44-3.39 (t, *J* = 7.32 Hz, $CH_3CH_2CH_2$, 2H), 3.17 (s, CH_2, 2H), 1.50-1.37 (m, $CH_3CH_2CH_2$, 2H), 0.78-0.73 (t, *J* = 7.32 Hz, $CH_3CH_2CH_2$, 3H); ^{13}C NMR ($CDCl_3$): δ 167.9, 167.0, 134.7, 129.0, 128.4, 127.6, 47.1, 44.8, 36.5, 20.4, 11.0; Mass spectrum (EI) m/z 232.0 (M^+) Exact mass calcd for $C_{13}H_{16}N_2O_2$: m/z 232.1212; found 232.1211.

4-7-1d: 1-Benzyl-2-ethoxycarbonylmethylpyrazolidine-3,5-dione. ^{1}H NMR ($CDCl_3$): δ 7.30-7.16 (m, *ArH*, 5H), 4.71 (s, $ArCH_2$, 2H), 4.10 (s, CH_2N, 2H), 4.00-3.93 (q, *J* = 7.08 Hz, CH_3CH_2, 2H), 3.26 (s, CH_2, 2H), 1.11-1.06 (t, *J* = 7.14 Hz, CH_3CH_2, 3H); ^{13}C NMR ($CDCl_3$): δ 170.3, 167.0, 166.4, 134.7, 128.8, 128.2, 127.5, 61.9, 47.5, 46.2, 36.1, 13.8; Mass spectrum (EI) m/z 276.1 (M^+) Exact mass calcd for $C_{14}H_{16}N_2O_4$: m/z 276.1110; found 276.1114.

4-7-1e: 1,2-Dibenzylpyrazolidine-3,5-dione. ^{1}H NMR ($CDCl_3$): δ 7.32-7.13 (m, *ArH*, 10H), 4.68 (s, $ArCH_2$, 4H), 3.31 (s, CH_2, 2H); ^{13}C NMR ($CDCl_3$): δ 166.9, 134.6, 128.9, 128.2, 127.3, 46.7, 36.4; Mass spectrum (EI) m/z 280.1 (M^+) Exact mass calcd for $C_{17}H_{16}N_2O_2$: m/z 280.1212; found 280.1219.

4-7-1f: 1-(2,4-Dimethoxybenzyl)-2-methylpyrazolidine-3,5-dione. ^{1}H NMR ($CDCl_3$): δ

7.16-6.40 (m, *ArH*, 3H), 4.79 (s, Ar*CH*$_2$, 2H), 3.80-3.79 (d, O*CH*$_3$, 6H), 3.17 (s, *CH*$_2$, 2H), 3.06 (s, *CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 167.6, 167.3, 161.1, 158.3, 130.6, 114.9, 104.6, 98.5, 55.4, 55.3, 42.2, 36.4, 30.5; Mass spectrum (ESI) m/z 263.3 ($M\text{-}H^+$) Exact mass calcd for $C_{13}H_{15}N_2O_4$: m/z 263.1032; found 263.1033.

4-7-1g: 2-Benzyl-1-(2,4-dimethoxybenzyl)pyrazolidine-3,5-dione. ^{1}H NMR ($CDCl_3$): δ 7.35-6.44 (m, *ArH*, 8H), 4.69 (s, Ar*CH*$_2$, 4H), 3.80-3.80 (d, O*CH*$_3$, 6H), 3.23 (s, *CH*$_2$, 2H); ^{13}C NMR ($CDCl_3$): δ 167.6, 167.3, 161.0, 158.2, 134.8, 130.4, 128.7, 128.1, 127.5, 114.7, 104.6, 98.5, 55.3, 55.2, 46.5, 42.2, 36.5; Mass spectrum (ESI) m/z 363.2 ($M+Na^+$) Exact mass calcd for $C_{19}H_{20}NaN_2O_4$: m/z 363.1321; found 363.1310.

4-7-1h: 2-Allyl-1-propylpyrazolidine-3,5-dione. ^{1}H NMR ($CDCl_3$): δ 5.82-5.69 (m, CH_2*CH*CH_2N, 1H), 5.30-5.24 (m, *CH*$_2$$CHCH_2$N, 2H), 4.21-4.19 (d, *J* = 5.91 Hz, CH_2CH*CH*$_2$N, 2H), 3.56-3.51 (t, *J* = 7.31 Hz, CH_3CH_2*CH*$_2$N, 2H), 3.17 (s, *CH*$_2$, 2H), 1.65-1.52 (m, CH_3*CH*$_2$$CH_2$N, 2H), 0.91-0.86 (t, *J* = 7.31 Hz, *CH*$_3$$CH_2CH_2$N, 3H); ^{13}C NMR ($CDCl_3$): δ 167.8, 167.0, 130.9, 119.5, 45.7, 44.4, 36.3, 20.4, 11.0; Mass spectrum (EI) m/z 182.0 (M^+) Exact mass calcd for $C_9H_{14}N_2O_2$: m/z 182.1055; found 182.1055.

4-7-1i: 2-Benzyl-1-propylpyrazolidine-3,5-dione. ^{1}H NMR ($CDCl_3$): δ 7.38-7.24 (m, *ArH*, 5H), 4.81 (s, Ar*CH*$_2$, 2H), 3.50-3.46 (t, *J* = 7.32 Hz, CH_3CH_2*CH*$_2$N, 2H), 3.24 (s, *CH*$_2$, 2H), 1.57-1.44 (m, CH_3*CH*$_2$$CH_2$N, 2H), 0.85-0.80 (t, *J* = 7.49 Hz, *CH*$_3$$CH_2CH_2$N, 3H); ^{13}C NMR ($CDCl_3$): δ 167.8, 167.0, 134.7, 128.9, 128.3, 127.6, 47.1, 44.7, 36.5, 20.4, 10.9; Mass spectrum (EI) m/z 232.0 (M^+) Exact mass calcd for $C_{13}H_{16}N_2O_2$: m/z 232.1212; found 232.1207.

4-7-2b: 2-Allyl-1-benzyl-4-ethoxycarbonylpyrazolidine-3,5-dione. ^{1}H NMR (CD_3OD, 500

MHz): δ 7.21-7.18 (m, *ArH*, 5H), 5.68-5.60 (m, CH_2*CH*CH_2N, 1H), 5.12-5.04 (m, *CH*$_2$CHCH$_2$N, 2H), 4.74 (s, Ar*CH*$_2$, 2H), 4.25-4.20 (q, *J* = 7.14 Hz, CH$_3$*CH*$_2$, 2H), 4.08-4.07 (d, *J* = 5.70 Hz, CH$_2$CH*CH*$_2$N, 2H), 1.28-1.25 (t, *J* = 7.25 Hz, *CH*$_3$CH$_2$, 3H); ^{13}C NMR (CD$_3$OD, 126 MHz): δ 171.7, 171.6, 169.3, 138.2, 133.9, 129.4, 128.9, 128.4, 118.3, 83.2, 60.6, 47.9, 47.2, 15.0; Mass spectrum (ESI) m/z 325.2 (M+Na$^+$) Exact mass calcd for $C_{16}H_{18}NaN_2O_4$: m/z 325.1164; found 325.1172.

4-7-2c: 1-Benzyl-4-ethoxycarbonyl-2-propylpyrazolidine-3,5-dione. ^{1}H NMR (CD$_3$OD): δ 7.22 (s, *ArH*, 5H), 4.77 (s, Ar*CH*$_2$, 2H), 4.27-4.20 (q, *J* = 7.08 Hz, CH$_3$*CH*$_2$, 2H), 3.47 (s, CH$_3$CH$_2$*CH*$_2$N, 2H), 1.47-1.40 (m, CH$_3$*CH*$_2$CH$_2$N, 2H), 1.30-1.25 (t, *J* = 6.98 Hz, *CH*$_3$CH$_2$, 3H), 0.77-0.72 (t, *J* = 7.32 Hz, *CH*$_3$CH$_2$CH$_2$N, 3H); ^{13}C NMR (CD$_3$OD): δ 171.8, 171.3, 169.4, 138.3, 129.4, 128.9, 128.5, 83.0, 60.5, 47.9, 45.8, 21.5, 15.0, 11.5; Mass spectrum (ESI) m/z 327.1 (M+Na$^+$) Exact mass calcd for $C_{16}H_{20}NaN_2O_4$: m/z 327.1321; found 327.1334.

4-7-2d: 1-(2,4-Dimethoxybenzyl)-4-ethoxycarbonyl-2-methylpyrazolidine-3,5-dione. ^{1}H NMR (CD$_3$OD): δ 7.05-6.31 (m, *ArH*, 3H), 4.76 (s, Ar*CH*$_2$, 2H), 4.27-4.20 (q, *J* = 6.97 Hz, CH$_3$*CH*$_2$, 2H), 3.80 (s, O*CH*$_3$, 3H), 3.71 (s, O*CH*$_3$, 3H), 3.01 (s, *CH*$_3$, 3H), 1.29-1.25 (t, *J* = 6.78 Hz, *CH*$_3$CH$_2$, 3H); ^{13}C NMR (CD$_3$OD): δ 171.8, 170.6, 169.8, 162.0, 159.6, 131.2, 118.2, 105.7, 99.0, 82.6, 61.2, 55.9, 55.7, 41.7, 31.4, 14.9; Mass spectrum (ESI) m/z 335.4 (M-H$^+$) Exact mass calcd for $C_{16}H_{19}N_2O_6$: m/z 335.1243; found 335.1246.

4-7-2e: 2-Benzyl-1-(2,4-dimethoxybenzyl)-4-ethoxycarbonylpyrazolidine-3,5-dione. ^{1}H NMR (CD$_3$OD): δ 7.16-6.23 (m, *ArH*, 8H), 4.68-4.65 (d, Ar*CH*$_2$, 4H), 4.24-4.17 (q, *J* = 6.96 Hz, CH$_3$*CH*$_2$, 2H), 3.77 (s, O*CH*$_3$, 3H), 3.70 (s, O*CH*$_3$, 3H), 1.26-1.22 (t, *J* = 7.14 Hz, *CH*$_3$CH$_2$, 3H); ^{13}C NMR (CD$_3$OD): δ 171.4, 171.0, 169.3, 161.8, 159.4, 138.2, 131.2, 129.3,

128.8, 128.3, 118.2, 105.7, 99.0, 83.4, 60.6, 55.8, 55.7, 47.6, 41.3, 15.0; Mass spectrum (ESI) m/z 411.2 ($M-H^+$) Exact mass calcd for $C_{22}H_{23}N_2O_6$: m/z 411.1556; found 411.1552.

4-7-2f: 2-Benzyl-4-ethoxycarbonyl-1-propylpyrazolidine-3,5-dione. ^{1}H NMR (CD_3OD): δ 7.22 (s, *ArH*, 5H), 4.78 (s, Ar*CH*$_2$, 2H), 4.26-4.19 (q, *J* = 6.96 Hz, CH_3*CH*$_2$, 2H), 3.51-3.46 (t, *J* = 6.74 Hz, CH_3CH_2*CH*$_2$N, 2H), 1.48-1.41 (m, CH_3*CH*$_2CH_2$N, 2H), 1.29-1.24 (t, *J* = 7.07 Hz, *CH*$_3CH_2$, 3H), 0.77-0.73 (t, *J* = 6.83 Hz, *CH*$_3CH_2CH_2$N, 3H); ^{13}C NMR (CD_3OD): δ 172.5, 170.6, 169.6, 138.0, 129.4, 128.9, 128.6, 82.7, 61.2, 47.8, 45.7, 21.5, 14.9, 11.5; Mass spectrum (ESI) m/z 327.1 ($M+Na^+$) Exact mass calcd for $C_{16}H_{20}NaN_2O_4$: m/z 327.1321; found 327.1334.

4-7-2g: 1-Benzyl-4-cyano-2-methylpyrazolidine-3,5-dione. ^{1}H NMR ($CDCl_3$): δ 7.32-7.19 (m, *ArH*, 5H), 4.99 (s, Ar*CH*$_2$, 2H), 3.21 (s, *CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 164.2, 164.1, 134.6, 129.0, 128.3, 127.2, 112.6, 64.4, 47.1, 30.7; Mass spectrum (EI) m/z 229.0 (M^+) Exact mass calcd for $C_{11}H_{11}N_3O_2$: m/z 229.0851; found 229.0818.

4-7-2h: 1-Benzyl-4-cyano-2-propylpyrazolidine-3,5-dione. ^{1}H NMR ($CDCl_3$): δ 7.24-7.11 (m, *ArH*, 5H), 4.88 (s, Ar*CH*$_2$, 2H), 3.53-3.48 (t, *J* = 7.31 Hz, CH_3CH_2*CH*$_2$, 2H), 1.38-1.29 (m, CH_3*CH*$_2CH_2$, 2H), 0.67-0.62 (t, *J* = 7.32 Hz, *CH*$_3CH_2CH_2$, 3H); ^{13}C NMR ($CDCl_3$): δ 164.9, 164.0, 134.6, 128.8, 128.1, 127.1, 112.3, 64.8, 47.4, 45.7, 21.1, 10.7; Mass spectrum (EI) m/z 257.0 (M^+) Exact mass calcd for $C_{14}H_{15}N_3O_2$: m/z 257.1164; found 257.1162.

4-7-2i: 1,2-Dibenzyl-4-cyanopyrazolidine-3,5-dione. ^{1}H NMR (DMSO-d_6): δ 7.28-7.13 (m, *ArH*, 10H), 4.45 (s, Ar*CH*$_2$, 4H); ^{13}C NMR (DMSO-d_6): δ 164.6, 134.4, 128.8, 128.0, 127.0, 112.6, 65.1, 47.6; Mass spectrum (EI) m/z 305.0 (M^+) Exact mass calcd for $C_{18}H_{15}N_3O_2$: m/z 305.1164; found 305.1165.

4-7-2j: 1-Benzyl-2-methyl-4-(4-nitrophenyl)pyrazolidine-3,5-dione. ^{1}H NMR (DMSO-d_6): δ 8.35-8.32 (d, *J* = 9.06 Hz, *ArH*, 2H), 8.10-8.07 (d, *J* = 9.06 Hz, *ArH*, 2H), 7.33-7.21 (m, *ArH*, 5H), 4.80 (s, Ar*CH*$_2$, 2H), 3.04 (s, *CH*$_3$, 3H); ^{13}C NMR (DMSO-d_6): δ 166.0, 165.6, 142.1, 141.9, 136.5, 128.4, 127.8, 127.5, 123.6, 123.5, 46.9, 40.9, 32.3; Mass spectrum (EI) m/z 325.1 (M^+) Exact mass calcd for $C_{17}H_{15}N_3O_4$: m/z 325.1063; found 325.1061.

4-7-2k: 1,2-Dibenzyl-4-(4-nitrophenyl)pyrazolidine-3,5-dione. ^{1}H NMR (DMSO-d_6): δ 8.42-8.39 (d, *J* = 9.06 Hz, *ArH*, 2H), 8.05-8.02 (d, *J* = 9.06 Hz, *ArH*, 2H), 7.33-7.18 (m, *ArH*, 10H), 4.67 (s, Ar*CH*$_2$, 4H); ^{13}C NMR (DMSO-d_6): δ 168.0, 144.2, 140.5, 137.0, 128.2, 128.1, 127.2, 123.5, 122.1, 47.0, 41.0; Mass spectrum (EI) m/z 401.1 (M^+) Exact mass calcd for $C_{23}H_{19}N_3O_4$: m/z 401.1376; found 401.1379.

4-7-3b: 4-Allyl-1-benzyl-4-ethoxycarbonyl-2-methylpyrazolidine-3,5-dione. ^{1}H NMR ($CDCl_3$): δ 7.38-7.29 (m, *ArH*, 5H), 5.63-5.49 (m, CH_2*CH*CH_2C, 1H), 5.26-4.66 (m, Ar*CH*$_2$, and *CH*$_2$CHCH$_2$C, 4H), 4.25-4.18 (q, *J* = 7.20 Hz, CH$_3$*CH*$_2$, 2H), 3.10 (s, N2*CH*$_3$, 3H), 2.99-2.86 (m, CH$_2$CH*CH*$_2$C, 2H), 1.27-1.23 (t, *J* = 7.14 Hz, *CH*$_3$CH$_2$, 3H); ^{13}C NMR ($CDCl_3$): δ 167.1, 166.1, 164.3, 134.4, 130.0, 128.9, 128.4, 127.8, 121.2, 77.21, 62.8, 46.6, 35.4, 30.7, 13.9; Mass spectrum (EI) m/z 316.1 (M^+) Exact mass calcd for $C_{17}H_{20}N_2O_4$: m/z 316.1423; found 316.1421.

4-7-3c: 1,4-Dibenzyl-4-ethoxycarbonyl-2-methylpyrazolidine-3,5-dione. ^{1}H NMR ($CDCl_3$): δ 7.29-6.90 (m, *ArH*, 10H), 4.85-4.45 (m, N1*CH*$_2$, 2H), 4.30-4.23 (q, *J* = 7.19 Hz, CH$_3$*CH*$_2$, 2H), 3.52-3.51 (d, *J* = 2.43 Hz, Ar*CH*$_2$, 2H), 2.69 (s, N2*CH*$_3$, 3H), 1.31-1.26 (t, *J* = 7.14 Hz, *CH*$_3$CH$_2$, 3H); ^{13}C NMR ($CDCl_3$): δ 167.1, 165.6, 164.5, 134.2, 133.8, 130.3, 128.7, 128.5, 128.1, 127.5, 127.1, 77.2, 62.9, 46.1, 37.0, 30.6, 13.9; Mass spectrum (EI) m/z 366.2 (M^+)

Exact mass calcd for $C_{21}H_{22}N_2O_4$: m/z 366.1580; found 366.1580.

4-7-3d: 4-Cyano-1,2-di(4-methoxybenzyl)-4-methylpyrazolidine-3,5-dione. ^{1}H NMR ($CDCl_3$): δ 7.15-6.88 (m, *ArH*, 8H), 4.69 (s, Ar*CH*$_2$, 4H), 3.82 (s, O*CH*$_3$, 6H), 1.72 (s, *CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 164.3, 160.0, 129.0, 128.2, 125.5, 114.7, 77.2, 55.3, 47.0, 19.8; Mass spectrum (EI) m/z 380.4 (M^+) Exact mass calcd for $C_{21}H_{21}N_3O_4$: m/z 379.1532; found 379.1534.

4-7-3e: 4-Benzyl-4-cyano-1,2-di(4-methoxybenzyl)pyrazolidine-3,5-dione. ^{1}H NMR ($CDCl_3$): δ 7.43-6.63 (m, *ArH*, 13H), 4.55-4.29 (m, N*CH*$_2$, 4H), 3.79 (s, O*CH*$_3$, 6H), 3.62 (s, Ar*CH*$_2$, 2H); ^{13}C NMR ($CDCl_3$): δ 161.8, 159.6, 131.7, 130.7, 129.0, 128.5, 128.1, 125.4, 114.4, 113.2, 77.2, 55.3, 46.6, 38.8; Mass spectrum (EI) m/z 455.3 (M^+) Exact mass calcd for $C_{27}H_{25}N_3O_4$: m/z 455.1845; found 455.1850.

4-7-3f: 1-Benzyl-2,4-dimethyl-4-(4-nitrophenyl)pyrazolidine-3,5-dione. ^{1}H NMR ($CDCl_3$): δ 8.20-8.17 (d, *J* = 9.06 Hz, C*ArH*, 2H), 7.71-7.68 (d, *J* = 8.70 Hz, C*ArH*, 2H), 7.34-7.21 (m, *ArH*, 5H), 4.91 (s, Ar*CH*$_2$, 2H), 3.21 (s, N2*CH*$_3$, 3H), 1.73 (s, C*CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 171.2, 170.9, 147.5, 143.2, 134.4, 129.1, 128.7, 127.8, 127.7, 123.8, 51.2, 46.9, 30.6, 22.5; Mass spectrum (EI) m/z 339.1 (M^+) Exact mass calcd for $C_{18}H_{17}N_3O_4$: m/z 339.1219; found 339.1213.

4-7-3g: 4-Benzyl-1,2-di(4-methoxybenzyl)-4-(4-nitrophenyl)pyrazolidine-3,5-dione. ^{1}H NMR ($CDCl_3$): δ 8.25-8.23 (d, *J* = 8.73 Hz, C*ArH*, 2H), 7.99-7.96 (d, *J* = 9.06 Hz, C*ArH*, 2H), 7.40-7.35 (m, CCH_2*ArH*, 5H), 6.65-6.51 (NCH_2*ArH*, 8H), 4.55-4.32 (m, N*CH*$_2$, 4H), 3.76 (s, O*CH*$_3$, 6H), 3.51 (s, C*CH*$_2$, 2H); ^{13}C NMR ($CDCl_3$): δ 168.8, 159.3, 147.5, 142.8, 134.6, 130.7, 128.8, 128.7, 128.2, 127.7, 126.1, 123.8, 114.1, 58.4, 55.2, 46.2, 43.1; Mass

spectrum (EI) m/z 551.4 (M^+) Exact mass calcd for $C_{32}H_{29}N_3O_6$: m/z 551.2056; found 551.2058.

4.5 References

[1] Lednice, D.; Mitschner, L. A. *The Organic Chemistry of Drug Synthesis*. John Wiley and Sons: New York, 1977, 234-238.

[2] (a) Stenzl, H. U. S. Patent. 2562830, **1951.** (b) Brooks, P. M.; Walker, J. J.; Dick, W. C.; Anderson, J. A.; Foler, P. D. *Br. J. Clin. Pharmacol.* **1975**, *2,* 437-442. (c) Domenjoz, R. *Ann. N. Y. Acad. Sci*. **1960**, *86,* 263-291.

[3] (a) Pfister, R.; Häfliger, F. *Helv. Chim. Acta*, **1957**, *40,* 395-401. (b) Showa, U.; Katsuhiko, S. *Nippon Nogeik. Kaishi*. **1963**, *59,* 335-347**.**

[4] (a) Puscas, I.; Coltau, M.; Pasca, R. *J. Pharmacol. Exp. Ther.* **1996**, *277,* 1464-1466. (b) Deuss, R.; Pfister, R.; Häfliger, F. U .S. Patent. 2910481, **1959**.

[5] (a) Walter, E.; Staiger, C. J.; De Vries, J.; Zimmermann, R.; Weber, E. *Eur. J. Clin. Pharmacol.* **1981**, *19,* 353-358. (b) Pfister, R.; Häfliger, F. *Helv. Chim. Acta*, **1961**, *44,* 232-237.

[6] (a) Buchanan, M. R. *Thromb. Res. Suppl.* **1983**, *4,* 89-92. (b) Margulies, E. H.; White, A. M.; Sherry, S. *Drugs.* **1980**, *20*, 179-197. (c) Kuzell, W. C.; Schaffarzick, R. W.; Brown, B.; Mankle, E. A. *J. Am. Med. Assoc.* **1952**, *149*, 729-734. (d) Margulies, E. H.; White, A. M.; Sherry, S.; *N. Engl. J. Med.* **1978**, *298*, 289-295. (e) El-Rayyes, N. R.; AI-Awadi, N. A. *Synthesis*, **1985**, 1028-1042.

[7] Krogdal, T. G. WO2000054771, **2000**.

[8] Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Nusinoff-Lehrman, S.; Gallo, R. C.; Bolognesi, D., Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 7096-7100.

[9] (a) Michel, K.; Matter, M. *Helv. Chim. Acta.* **1961**, *44*, 1025-1030. (b) Schatz, F.; Wagner-Jauregg, T. *Helv. Chim. Acta.* **1968**, *51*, 1919-1031. (c) Franz P, D.; Gerwalt, Z.; *Chem. Ber*. **1975**, *108*, 2189-2201. (d) Bellora, E.; Marazzi-Uberti, E.; Gallazzi, A.; Donetti, A. *Farmaco.* **1981**, *36*, 432-440. (e) Rahtz, D.; Baettcher, I. *Eur. J. Med. Chem.* **1982**, *17*, 429-432. (f) Gruetzmacher, H. F.; Schmiegel, J. *Chem. Ber.* **1989**, *122*, 1929-1933. (g) Kende, A. S.; Koch, K.; Smith, C. A. *J. Am. Chem. Soc*. 1988, *110*, 2210-2218. (h) Song, Y.; Guo, Y.; Lin, S.; Jin, S. *Beijing Daxue Xuebao, Ziran Kexueban*. **1987**, *2*, 48-53. (i) Vennerstrom, J. L.; Holmes, T. J. *J. Med. Chem.* 1987, *30*, 563-567.

[10] Graziano, B.; Michele, G. *Tetrahedron*. **1995**, *51*, 9487-9492.

[11] (a) Dubau, F. P. *Chem. Ber*. **1983**, *116*, 2714-2716. (b) Fritsch, G.; Zinner, G.; Beimel, M.; Mootz, D.; Wunderlich, H. *Pharmazie* **1986**, *319*, 70-78.

[12] (a) Lawton, G.; Moody, C. J.; Pearson, C. J. *J. Chem. Soc., Perkin Trans. 1.* **1987**, 877-884. (b) Lawton, G.; Moody, C. J.; Pearson, C. J.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1.* **1987**, 885-896.

[13] He, R.; Lam, Y. *J. Comb. Chem.* **2005**, *7*, 916-920.

[14] Zhao, X-Y.; Metz, W. A.; Sieber, F.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 8433-8436.

Chapter 5 Development of a Polymer-Supported Hantzsch Ester

5.1 Introduction

The synthesis of organic compounds using polymer-supported reagents and catalysts,[1] has been of great interest in recent years, especially in pharmaceutical research community.[2] Organic synthesis using polymer-supported reagents and catalysts offers a number of advantages over traditional solution-phase synthesis. The first and most important advantage is the easy separation of the supported and non-supported species by filtration at the end of the reaction. This greatly simplifies purification processes, such as column chromatography, distillation or recrystallization. In addition, high concentrations of reagents can be used to drive the reaction to completion as byproducts or excess reagents can be easily removed. The reagents and catalysts recovered could, at times, be recycled, thus reducing the cost of the synthesis.[3] The second advantage involves safety consideration. Chemicals are always thought to be toxic, odorous and harmful. If they were immobilized to a polymer, they would be much easier and safer to handle. Since they are less toxic and non-odorous, the synthesis involving them will be more environmentally benign.[4] The third advantage concerns the unique microenvironment created within the polymer, which could improve the performance of reagents or catalysts in reactions. It has been reported that polymer-supported catalysts have improved stability,[5] increased selectivity,[6] enhanced regioselectivity due to steric hindrance,[7] and could possess superior activity due to site cooperation.[8]

5.1.1 Soluble polymer-supported reagents and catalysts

There are two kinds of polymer-supported reagents and catalysts, those that are immobilized to insoluble polymers and those that are immobilized to soluble polymers. Initially, soluble

polymer supports did not receive as much attention as their cross-linked insoluble counterparts.[9] However, the heterogeneous reaction condition associated with using insoluble polymers presents several limitations, for example nonlinear kinetic behavior, unequal distribution or access to chemical reactions, solvation problems, and synthetic difficulties in transferring standard organic reactions to the solid-phase. Thus soluble polymers as supports have received significant attention in recent years.[9] As soluble polymers dissolve in specific solvents and precipitate out when other solvents are added, reactions with them combine the advantages of insoluble polymer-supported synthesis with traditional solution-phase synthesis. To date, various soluble polymer-supported reagents and catalysts have been developed. These include phosphines,[10] Swern oxidant,[11] borane complex,[12] alkali metal,[13] amorphous selenium,[14] hydrogenation catalysts,[15] chinchona alkaloid ligands for the Sharpless asymmetric dihydroxylation,[16] epoxidation catalysts,[17] and so on. These polymer-supported reagents and catalysts have been immobilized on different kinds of polymer supports so that they can be applied under different reaction conditions.

5.1.1.1 Soluble polymer supports

Many types of polymers have been used as supports for immobilizing reagents and catalysts. These include polystyrene, polyvinyl alcohol, polyethylene imine, polyacrylic acid, polyacrylamide, polymethylene oxide, PEG, polypropylene oxide, cellulose, and so on.[18] Amongst them, non-cross-linked polystyrene and PEG are the most commonly used polymeric supports.

Non-cross-linked polystyrene is readily prepared from styrene and AIBN. Its remarkable solubility properties make it extremely useful to organic synthesis. It is soluble in THF,

CH_2Cl_2, $CHCl_3$, benzene, toluene, DMF, acetone and EtOAc and is insoluble in H_2O and MeOH.

PEG is a linear polymer formed from the polymerization of ethylene oxide. It exhibits solubility in a wide range of solvents including DMF, CH_2Cl_2, toluene, MeCN, and H_2O, but is insoluble in hexane, Et_2O, *tert*-butyl methyl ether and isopropyl alcohol.[19]

5.1.1.2 Characterizations of soluble polymer-supported reagents and catalysts

Although the characterization of insoluble polymer-supported intermediates can be done by gel-phase MAS NMR and single bead IR, the inherent heterogeneity of solid-phase systems precludes the use of many traditional characterization methods. Soluble polymers do not suffer from this drawback and they can be characterized by many routine techniques such as NMR, UV-visible, IR, and high resolution mass spectroscopies. Circular dichroism measurements have also been used for analyzing PEG bound peptides.[20]

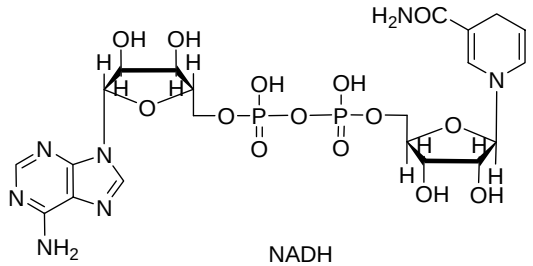
5.1.2 Hantzsch ester

Dihydropyridine chemistry began in 1882 when Hantzsch published the synthesis which now bears his name.[21] After the discovery in 1930s that a dihydropyridine (NADH, a dihydronicotinamide derivative) was a "hydrogen-transferring coenzyme" for oxidation and reduction in biological systems,[22] it has been a stimulus for using Hantzsch ester (Figure 5-1) and other 1,4-dihydropyridines as biomimic reducing agents in synthetic organic chemistry.[23] Evidence shows that they may reduce substrates by a one-step hydride transfer or by a multip-step electron-transfer-initiated hydride transfer.[23d,23e]

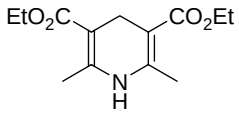
To date, dihydropyridines have been successfully applied for the reduction of ketones,[24] aldehydes[25] and α,β-unsaturated compounds.[26] They have also found applications in

asymmetric reductions[27] and reductive aminations.[28]

Figure 5-1 Structures of NADH and Hantzsch Ester



NADH

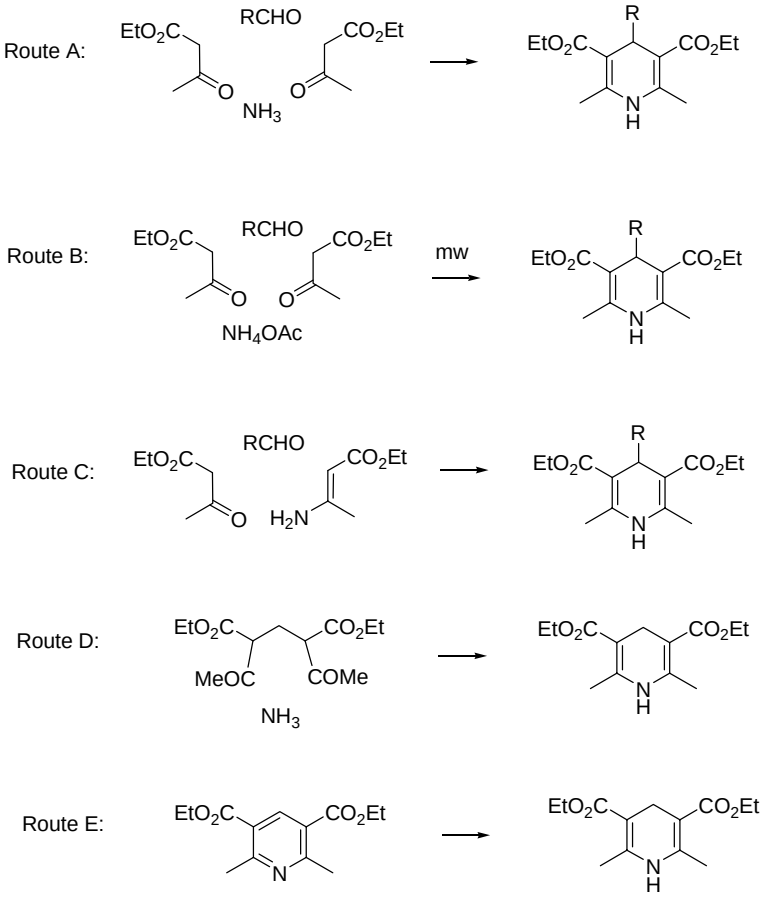


Hantzsch ester

In addition to their reducing function, Hantzsch ester and 1,4-dihydropyridines are an important class of calcium channel blockers and one of the most important class of drugs for the treatment of cardiovascular diseases.[29] Many compounds carrying a dihydropyridine heterocyclic ring are used as vasodilator, bronchodilator, antiatherosclerotic, antitumor, geroprotective, heptaprotective, and antidiabetic agents.[30]

In the original synthesis of Hantzsch ester,[21] an aldehyde, acetoacetic ester, and ammonium hydroxide were mixed together to give the product (Route A, Scheme 5-1). This classical method usually gave the products in low yields, especially when sterically hindered aldehydes were used. Several improved procedures have been reported[31a-31h] and these include a high yielding microwave-assisted synthesis of substituted 1,4-dihydropyridines (Route B, Scheme 5-1);[31e] condensation of an aldehyde, acetoacetic ester and ethyl 3-aminocrotonate in the absence of an ammonia source,[31f] reaction of 1,5-diketones with ammonia to yield Hantzsch ester spontaneously (Route D, Scheme 5-1)[31g] and the reduction of pyridine. (Route E, Scheme 5-1).[31h]

Scheme 5-1 Synthesis of Dihydropyridines and Hantzsch Ester



5.1.3 Objectives and scope of this study

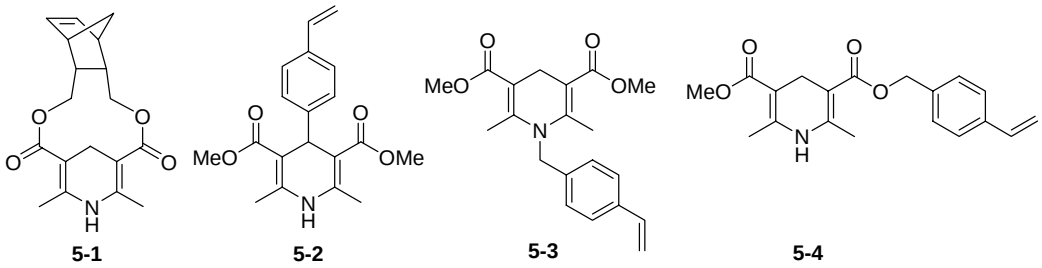
Although the Hantzsch ester has been widely used as a reductant in synthetic organic chemistry, the study of soluble polymer-supported Hantzsch ester has not been explored. Thus this project aims to develop a soluble polymer-supported Hantzsch ester and investigate its reductive properties.

5.2 Results and Discussion

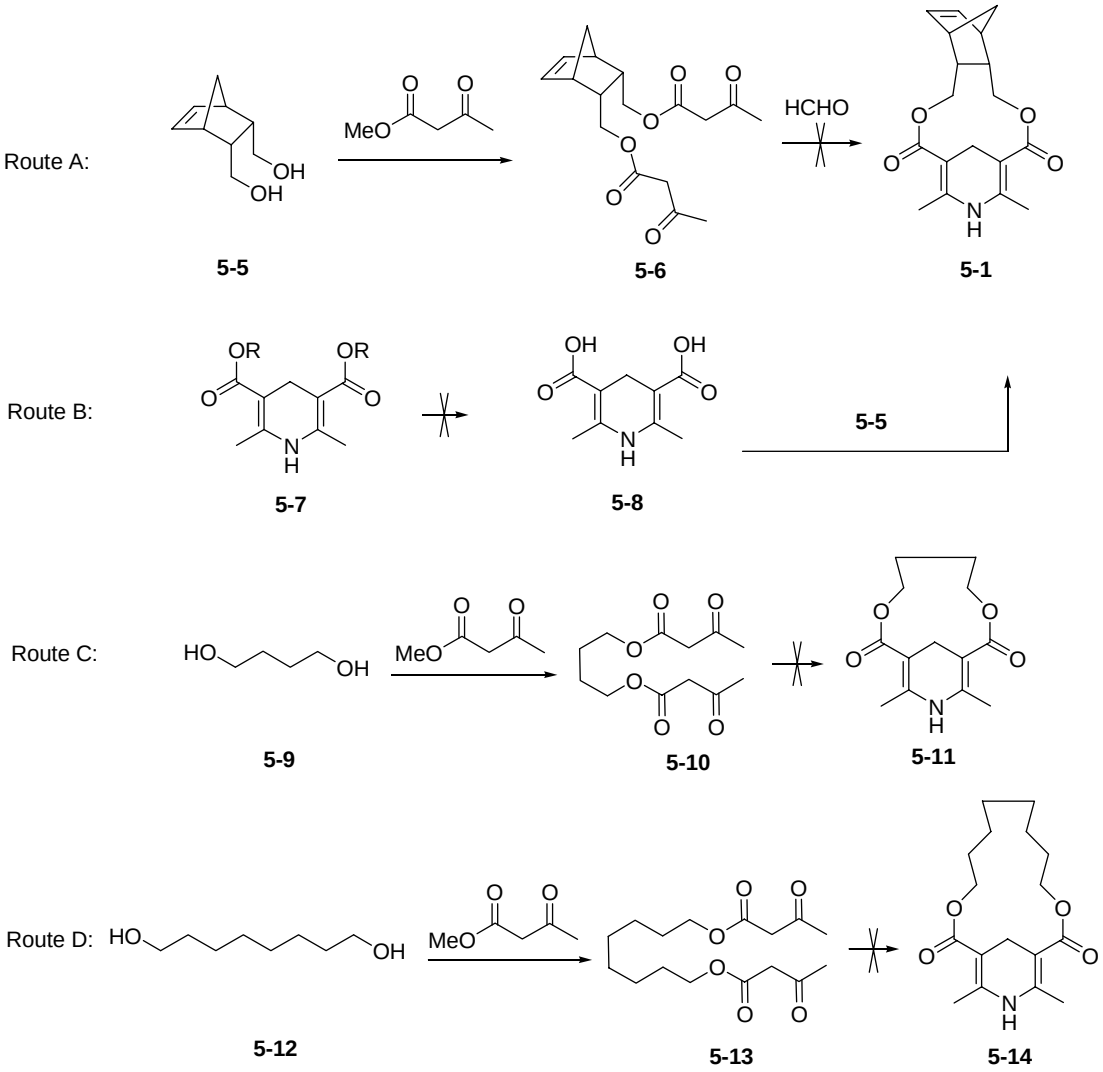
5.2.1 Design and synthesis of monomers

To begin our investigation, we had to design and prepare a monomer which contains a Hantzsch ester. Our first monomer design was **5-1**, a ROMP monomer (Figure 5-2), and two synthetic methods were designed for synthesizing it (Route A and B, Scheme 5-2). In the first method, although **5-6** could be easily prepared from **5-5**, attempts to synthesize **5-1** from **5-6** failed to give the desired product. The specific rigidity of the bridged structure of norbornene **5-6** and the short distance between the norbornene ring and keto ester were thought to be the reasons for the failed synthesis. To verify this hypothesis, we proceeded to synthesize analogues **5-11** and **5-14**. Although the precursors **5-10** and **5-13** could be prepared successfully, we were unable to effect the condensations to give **5-11** and **5-14**. We next explored the possibility of coupling a diacid **5-8** with a diol **5-5** (Route B, Scheme 5-2). However attempts to hydrolyze **5-8** to **5-7** were met with great difficulties. Since monomer **5-1** could not be synthesized satisfactorily, we decided to explore the possibility of using compound **5-2** in reductions. Compound **5-2** was synthesized in good yield by using Guo's method.[31e] However when it was applied to a reduction reaction, it did not show any reducing ability. This implied that for dihydropyridines to behave as a reductant in reduction, the C4 position could not be substituted. Substitution on N1, as shown in monomer **5-3**, was not advisable as a substituent at this position could affect the reactivity. Hence we eventually decided on compound **5-4** as our monomer for preparing a polymer-supported Hantzsch ester.

Figure 5-2 Structures of Monomers



Scheme 5-2 Synthesis of Monomer **5-1**

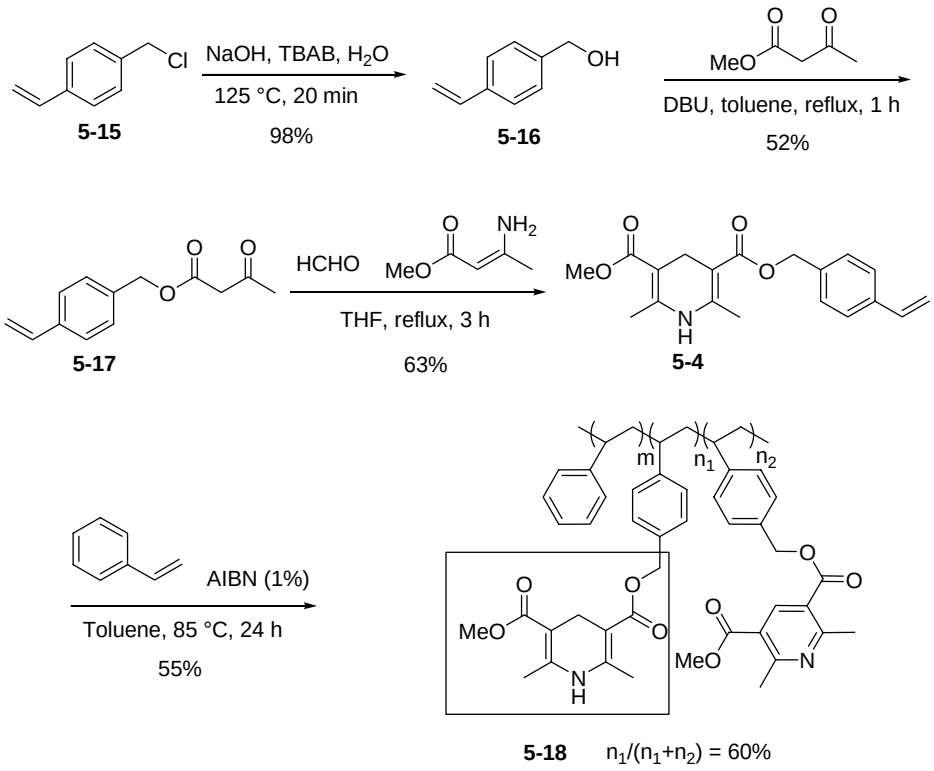


5.2.2 Synthesis of a polymer-supported Hantzsch ester

5.2.2.1 Synthesis of 4-vinylbenzyl alcohol (5-16)

In the initial synthesis of a polymer-supported Hantzsch ester, monomer **5-4** was prepared and copolymerized with styrene to give polymer **5-18** (Scheme 5-3).

Scheme 5-3 Synthesis of a Polymer-Supported Hantzsch Ester **5-18** via Monomer **5-4**



5-15 **5-16** **5-17** **5-4**

5-18 $n_1/(n_1+n_2) = 60\%$

Compound **5-16** was prepared by first hydrolyzing 4-vinylbenzyl chloride (**5-15**) to 4-vinylbenzyl alcohol (**5-16**). Unlike the hydrolysis of benzyl chloride which proceeded very efficiently, the hydrolysis of 4-vinylbenzyl chloride was complicated and gave byproduct (di-(4-vinylbenzyl) ether) easily. Different hydrolysis conditions were attempted to decrease the formation of the byproduct (Table 5-1) and the best result was obtained using NaOH (0.1 equiv) in H_2O and TBAB as phase-transfer catalyst (Entry 8, Table 5-1).

Table 5-1 Synthesis of **5-16**

Entry	*Reagent and Solvent*	*Conditions*	*Result*
1	NaOH (1 equiv),TBAB, H_2O	rt, 3 h	Reaction very slow
2	NaOH (1 equiv), TBAB, H_2O	95 °C, 110 °C, 130 °C, 10 min to 1 h	p: 24%-40%, byp: major
3	NaOH (2 equiv), TBAI, KI, H_2O	rt, 2 h	Reaction very slow
4	NaOH (2 equiv), TBAI, KI, H_2O	65 °C, 5 h	p: traces, byp: major
5	NaOH (2 equiv), H_2O, EtOH	rt, 24 h	p: 19%, byp: 81%
6	H_2O	reflux under N_2 3 h	p: 70%
7	NaOH (0.1 equiv), TBAB, H_2O	125 °C, 10 min	p: 58%, byp: traces, **5-15**: 37%
8	NaOH (0.1 equiv), TBAB, H_2O	125 °C, 20 min	p: 98%, byp: traces

5.2.2.2 Synthesis of 4-vinylbenzyl acetoacetate (5-17)

Compound **5-16** was then reacted with methyl acetoacetate in the presence of DBU to afford **5-17**. This reaction gave **5-17** in 52% yield when the mixture was refluxed for 2 h. Prolong heating time resulted in a lower yield due to the formation of byproducts.

5.2.2.3 Synthesis of 3-(4-vinylbenzyl)-5-methyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (5-4)

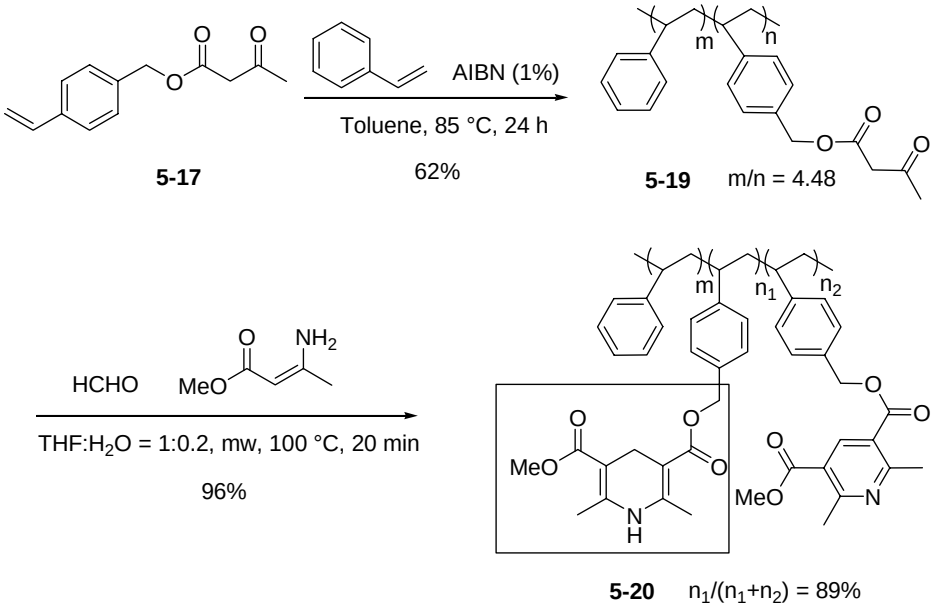
Using a modified version of the method described in Scheme 5-1, monomer **5-4** was prepared directly from **5-17** in 63% yield.

5.2.2.4 Synthesis of polymer 5-18

With monomer **5-4** in hand, we proceeded to copolymerize it with styrene by standard radical polymerization method. Analysis of this polymer-supported Hantzsch ester **5-18** by ^{1}H NMR

showed that 40% of the **5-18** had decomposed during the polymerization to its pyridine cousin, which does not have reducing ability (Scheme 5-3). This was not ideal because the active part of **5-18** was dramatically reduced. Since long heating time is often required in radical polymerization, we thought that it could be difficult to prevent Hantzsch ester decomposition during the polymerization of **5-4**. To circumvent this problem, we decided to polymerize **5-17** (Scheme 5-4).

Scheme 5-4 Synthesis of a Polymer-Supported Hantzsch Ester **5-20**



5-17 **5-19** m/n = 4.48

5-20 $n_1/(n_1+n_2)$ = 89%

5.2.2.5 Synthesis of polymer 5-19

Monomer **5-17** was copolymerized with styrene by standard radical polymerization method to give polymer-supported ketoester **5-19**. This product formation was amenable to KBr FTIR monitoring (i.e. the appearance of C=O stretch at 1744.2 cm^{-1} and 1719.7 cm^{-1}, indicating the presence of this product) and ^1H NMR. Through ^1H NMR analysis, the loading of ketoester in **5-19** could also be determined, and was found to be 1.562 mmol/g.

5.2.2.6 Synthesis of polymer 5-20

Efforts to synthesize polymer **5-20** by heating **5-19** with methyl 3-aminocrotonate and HCHO resulted in the decomposition of Hantzsch ester. Attempts to reduce the heating time gave an incomplete reaction. Inspired by Guo's synthesis,[31e] we thought that microwave irradiation could be a solution for this problem as it may shorten heating time thus could prevent the decomposition. Hence we carried out the reaction in THF and microwave irradiation. ^{1}H NMR monitoring showed that 20 min irradiation was required for **5-19** to be totally consumed and the resultant polymer was no better than the one obtained by normal heating (38% decomposition) (Entry 1, Table 5-2). After giving the reaction much thought, we realized that the presence of H_2O could possibly prevent the decomposition and speed up the reaction. Therefore different percentages of H_2O in THF were added to the reaction system and tested under microwave irradiation. We observed that small percentages such as one drop, 5%, 10% did not improve the results significantly (Entries 2, 3 and 4, Table 5-2). However, to our delight, 20% H_2O in THF gave a significantly better result and the decomposition product was dramatically reduced to a very low level (Entry 5, Table 5-2). Further experimentation, such as using shorter reaction time and higher reaction temperature did not provide better results (Entries 6 and 7, Table 5-2). Since polystyrene does not dissolve in H_2O, 20% was the maximum percentage of H_2O used in our reaction. Further addition of H_2O resulted in the precipitation of **5-19** from the reaction mixture and the reaction ceased under this condition.

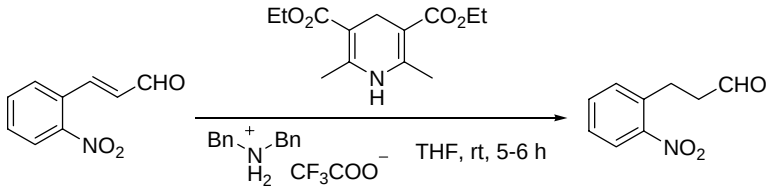
Table 5-2 Synthesis of Polymer **5-20**

Entry	*Solvent*	*Conditions*	*Result*
1	THF	mw, 100 °C, 20 min	$n_1/(n_1+n_2)$ = 62%
2	THF/H_2O (1 drop)	mw, 100 °C, 20 min	$n_1/(n_1+n_2)$ = 63%
3	THF:H_2O = 1:0.05	mw, 100 °C, 20 min	$n_1/(n_1+n_2)$ = 62%
4	THF:H_2O = 1:0.1	mw, 100 °C, 20 min	$n_1/(n_1+n_2)$ = 67%
5	THF:H_2O = 1:0.2	mw, 100 °C, 20 min	$n_1/(n_1+n_2)$ = 89%
6	THF:H_2O = 1:0.2	mw, 100 °C, 10 min	$n_1/(n_1+n_2)$ = 85%, traces of **5-19**
7	THF:H_2O = 1:0.2	mw, 120 °C, 5 min	$n_1/(n_1+n_2)$ = 82%, traces of **5-19**

5.2.3 Reduction of α,β-unsaturated aldehydes by polymer-supported Hantzsch ester

Recently List[26d] reported an organic ammonium salt catalyzed reduction of α,β-unsaturated aldehydes by using the Hantzsch ester (Scheme 5-5). To validate our polymer-supported Hantzsch ester, the reduction of α,β-unsaturated aldehydes was carried out.

Scheme 5-5 Reduction of α,β-Unsaturated Aldehydes by Hantzsch Ester



As shown in Scheme 5-6, *trans*-4-nitrocinnamaldehyde was reduced to its saturated counterpart **5-21a** using **5-20** as a reductant under a similar condition as that reported by List and the yield obtained was also comparable to the solution-phase reduction.[26d] However with **5-20**, the reaction needed 24 h to complete. Thus a screening was carried out to search for a better catalyst (Table 5-3). Four ammonium salt catalysts (Figure 5-3) were synthesized, and tested for this reduction. Reactions with catalysts **5A** and **5C** required a longer reaction time

than with **5B** and **5D**. Since catalyst **5D** was easier to prepare than **5B**, catalyst **5D** was chosen for the reduction of α,β-unsaturated aldehydes with **5-20**.

Scheme 5-6 Reduction of α,β-Unsaturated Aldehydes by Polymer **5-20**

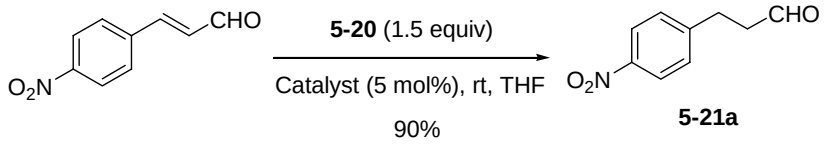


Figure 5-3 Catalysts for Reduction of α,β-Unsaturated Aldehydes

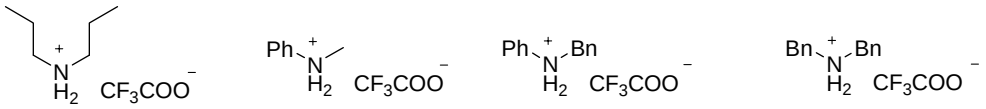


Table 5-3 Catalysts Screening for Reduction of α,β-Unsaturated Aldehydes

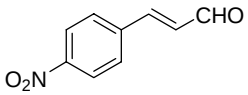
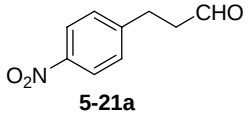
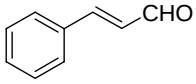
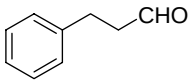
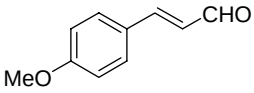
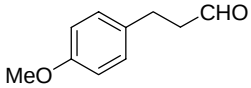
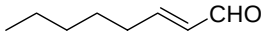
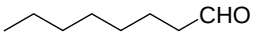
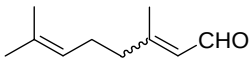
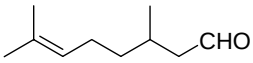
Entry	*Catalyst*	*Concentration of polymer **5-20***	*Time*	*Result (By TLC)*
1	**5A**	0.05 M	48 h	100% conversion
2	**5B**	0.05 M	24 h	100% conversion
3	**5C**	0.05 M	48 h	100% conversion
4	**5D**	0.05 M	24 h	100% conversion

A solvent screening with **5D** as catalyst was conducted to find the optimal solvent for this reaction (Table 5-4). CH_2Cl_2 was found to be the best solvent as the reaction was completed within 12 h. When the concentration of **5-20** was increased to 0.2 M (Entries 6 and 7, Table 5-4), the reaction was completed within 4 h. These conditions were more efficient than the ones used in the reported reduction[26d] where the concentration of the Hantzsch ester was 0.275 M and the reaction time was 5-6 h. Thus Entry 6 (Table 5-4) was selected as the standard conditions for further investigation of this reduction.

Table 5-4 Solvents Screening for Reduction of α,β-Unsaturated Aldehydes

Entry	*Solvent*	*Concentration of polymer **5-20***	*Time*	*Result (By GC)*
1	THF	0.05 M	12 h	52% conversion
2	CH_2Cl_2	0.05 M	12 h	100% conversion
3	$CHCl_3$	0.05 M	12 h	81% conversion
4	DMF	0.05 M	12 h	14% conversion
5	Toluene	0.05 M	12 h	82% conversion
6	CH_2Cl_2	0.1 M	7 h	100% conversion
7	CH_2Cl_2	0.2 M	4 h	100% conversion

Table 5-5 Reduction of α,β-Unsaturated Aldehydes

Entry	*Substrate*	*Product*	*Yield*
1		 **5-21a**	90%[a]
2		 **5-21b**	87%[a]
3		 **5-21c**	85%[a]
4		 **5-21d**	65% (5 h)[b] 94% (18 h)[b] 99% (23 h)[b]
5		 **5-21e**	99% (4 h)[c]

[a] Yield of isolated product. [b] Yield determined by GC. [c] Yield determined by GC-MS.

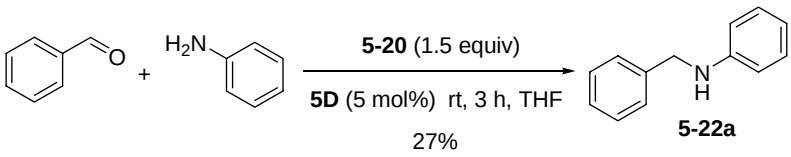
To prove the versatility of **5-20** in the reduction of α,β-unsaturated aldehydes, 5 different substrates were tested (Table 5-5). The results obtained showed that, in general, both aromatic and aliphatic substrates could be reduced to the corresponding saturated products in good yields within 4 h. These results imply that **5-20** was applicable for the reduction of

α,β-unsaturated aldehydes, and the ease of workup made it more practical than a non-supported Hantzsch ester.

5.2.4 Reductive amination by polymer-supported Hantzsch ester

Reductive amination with the Hantzsch ester has been studied by many research groups.[27e,27g,28] Various catalyst, such as Bronsted acids,[27e,27g] Lewis acids [Mg^{2+},[28a] SiO_2,[28b] Al_2O_3,[28b] $Sc(OTf)_3$[28c,28d]], and thiourea,[28e] have been used for this reaction. Generally, these reactions required a few hours to a few days to complete. To widen the application of **5-20**, we decide to conduct reductive amination with it. Prior to the reductive amination reaction, we carried out a search for a new catalyst which would improve the reaction condition. Reaction with catalyst **5D** gave the product in 27% yield after 3 h at rt (Scheme 5-7), which was not as good as the results obtained using reported catalysts.[30] Incidentally, we discovered that this reaction occurred rapidly in the presence of 1.5 M HCl to give the product in excellent yield (Scheme 5-8). Hence 1.5 M HCl was used to examine the reductive amination of various aldehydes and amines in the presence of **5-20** (Table 5-6).

Scheme 5-7 Reductive Amination by Polymer **5-20** with **5D**



Scheme 5-8 Reductive Amination by Polymer **5-20** with HCl

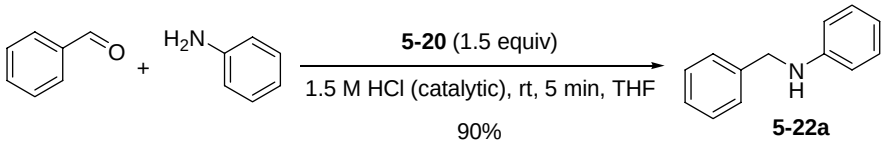
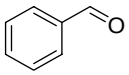
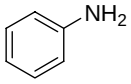
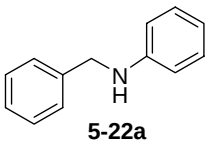
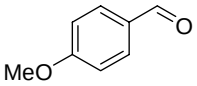
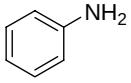
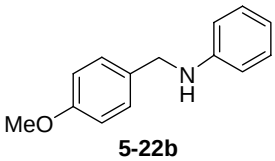
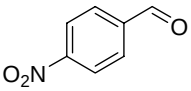
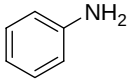
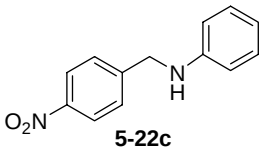
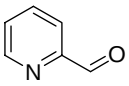
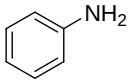
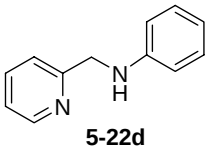
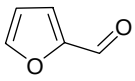
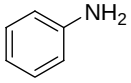
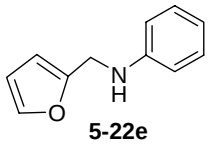
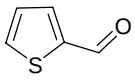
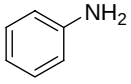
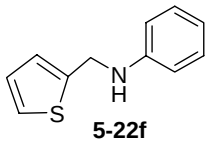
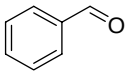
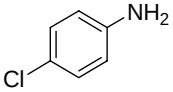
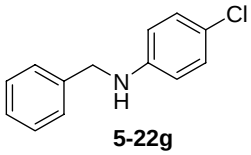
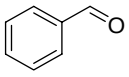
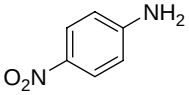
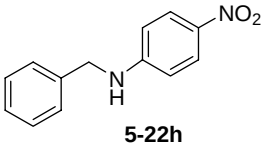
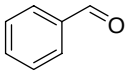
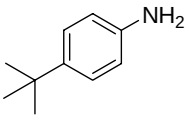
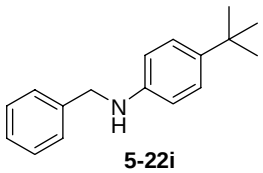


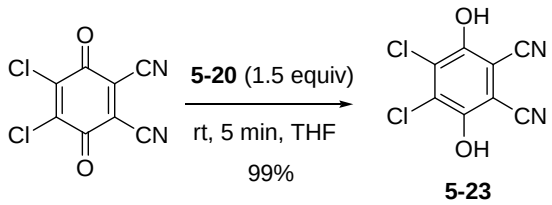
Table 5-6 Reductive Amination of Aldehydes and Amines

Entry	*Aldehyde*	*Amine*	*Product*	*Yield*
1			 **5-22a**	99%
2			 **5-22b**	87%
3			 **5-22c**	90%
4			 **5-22d**	91%
5			 **5-22e**	99%
6			 **5-22f**	97%
7			 **5-22g**	99%
8			 **5-22h**	96%
9			 **5-22i**	88%

5.2.5 Aromatization of benzoquinone by polymer-supported Hantzsch ester

To further prove the application of **5-20**, aromatization of an activated-benzoquinone was conducted and was found to be completed within 5 min at rt. The reaction did not require the use of a catalyst and the product was obtained in quantitative yield (Scheme 5-9).

Scheme 5-9 Aromatization of Benzoquinone



5-23

5.3 Conclusion

This project investigated the design, development and applications of a soluble polymer-supported Hantzsch ester as a reducing agent. An efficient synthetic method was discovered for the synthesis of this polymer-supported Hantzsch ester. The polymer-supported Hantzsch ester was successfully applied for the reduction of α,β-unsaturated aldehydes, reductive amination between aldehydes and aniline and reduction of benzoquinones.

5.4 Experimental

All chemical reagents were obtained from Aldrich, Merck, Lancaster or Fluka and used without further purification. Analytical TLC was carried out on pre-coated plates (Merck silica gel 60, F254) and visualized with UV light or stained with ninhydrin. CC was performed with silica (Merck, 70-230 mesh). ^{1}H NMR and ^{13}C NMR spectra were measured at 298 K on a Bruker DPX 300 or DPX 500 Fourier Transform spectrometer. Chemical shifts are reported in δ (ppm), relative to the internal standard of TMS. The signals observed are

described as: s, d, t, q, m. The number of protons (n) for a given resonance is indicated as nH. All Infra-red spectra were recorded on a Bio-Rad FTS 165 spectrometer. Mass spectra were performed on VG Micromass 7035 spectrometer under EI, Finnigan/MAT LCQ under ESI (Normal), and Finnigan/MAT 95XL-T under ESI (Accurate). GC analysis were performed on Agilent 6890 series GC system using column DB-1 (30 m x 250 μm x 0.25 μm) (Oven: 50 °C, Injector: 230 °C, Detector: 250 °C). GC-MS analysis were performed on Hewlett Packard 6890 series GC system integrated with HP 5973 mass selective detector using column ZB-1 (30 m x 250 μm x 0.25 μm) (Oven: 50 °C, Injector: 230 °C, Detector: 250 °C).

5.4.1 Synthesis of 4-vinylbenzyl alcohol (5-16)

To NaOH (0.04 g, 1 mmol) and TBAB (3.224 g, 10 mmol) in H_2O (50 mL) was added 4-vinylbenzyl chloride (1.409 mL, 10 mmol). The mixture was heated at 125 °C for 20 min and subsequently cooled in an ice-water bath. Upon cooling, the mixture was extracted with EtOAc (50 mL x 3) and the combined organic layer was dried with $MgSO_4$, filtered, concentrated and purified by CC (EtOAc:hexane = 1:5) to give **5-16** as a colorless oil (1.310 g, 98% yield). ^{1}H NMR ($CDCl_3$): δ 7.28-7.15 (m, *ArH*, 4H), 6.65-6.56 (m, *CH*CH_2, 1H), 5.67-5.61 (d, *J* = 17.4 Hz, CH*CH*$_2$, 1H), 5.16-5.12 (d, *J* = 10.8 Hz, CH*CH*$_2$, 1H), 4.48 (s, *CH*$_2$, 2H), 2.47 (s, *OH*, 1H); ^{13}C NMR ($CDCl_3$): δ 140.4, 136.8, 136.4, 127.1, 126.2, 113.7, 64.7; Mass spectrum (EI) m/z 133.9 (M^+) Exact mass calcd for $C_9H_{10}O$: m/z 134.0732; found 134.0732.

5.4.2 Synthesis of 4-vinylbenzyl acetoacetate (5-17)

To methyl acetoacetate (1.1 mL, 10.188 mmol), DBU (0.385 mL, 2.547 mmol) and toluene (30 mL) was added **5-16** (1.1393 g, 8.49 mmol) and the mixture was refluxed at 125 °C for 1

h. After which, another 1.1 mL methyl acetoacetate was added, and the mixture was further refluxed for 1 h and then concentrated and purified by CC (EtOAc:hexane = 1:5) to give **5-17** as a colorless oil (0.963 g, 52% yield). ^{1}H NMR ($CDCl_3$): δ 7.42-7.30 (m, *ArH*, 4H), 6.75-6.66 (m, *CH*CH_2, 1H), 5.79-5.73 (d, *J* = 17.4 Hz, CH*CH*$_2$, 1H), 5.28-5.25 (d, *J* = 10.8 Hz, CH*CH*$_2$, 1H), 5.16 (s, Ar*CH*$_2$, 2H), 3.49 (s, CO*CH*$_2$CO, 2H), 2.24 (s, *CH*$_3$, 3H); ^{13}C NMR ($CDCl_3$): δ 200.2, 166.8, 137.8, 136.2, 134.7, 128.6, 126.4, 114.4, 66.8, 50.0, 30.0; Mass spectrum (EI) m/z 218.0 (M^+) Exact mass calcd for $C_{13}H_{14}O_3$: m/z 218.0943; found 218.0946.

5.4.3 Synthesis of monomer 5-4

To compound **5-17** (0.8548 g, 3.917 mmol) in THF (20 mL) was added methyl 3-aminocrotonate (0.4548 g, 3.917 mmol) and HCHO (37% solution, 0.108 mL, 3.917 mmol). The mixture was refluxed for 3 h then concentrated and purified by CC (EtOAc:hexane = 1:3) to give **5-4** as a yellow solid (0.807 g, 63% yield). ^{1}H NMR ($CDCl_3$): δ 7.32-7.22 (m, *ArH*, 4H), 6.67-6.57 (m, *CH*CH_2, 1H), 5.69-5.63 (d, *J* = 17.8 Hz, CH*CH*$_2$, 1H), 5.18-5.14 (d, *J* = 10.8 Hz, CH*CH*$_2$, 1H), 5.07 (s, Ar*CH*$_2$, 2H), 3.60 (s, CO_2*CH*$_3$, 2H), 3.23 (s, *CH*$_2$, 2H), 2.09 (s, *CH*$_3$, 6H); ^{13}C NMR ($CDCl_3$): δ 168.4, 167.6, 145.7, 145.2, 141.0, 137.1, 136.4, 128.0, 126.2, 113.9, 99.2, 98.9, 65.1, 50.9, 24.8, 19.1, 18.9; Mass spectrum (EI) m/z 327.3 (M^+) Exact mass calcd for $C_{19}H_{21}NO_4$: m/z 327.1471; found 327.1470.

5.4.4 Synthesis of polymer 5-18

To monomer **5-4** (0.5 g, 1.53 mmol) and styrene (1.05 mL, 9.13 mmol) in toluene (8.7 mL) was added AIBN (0.0175 g, 0.1066 mmol). The mixture was purged with N_2 at rt for 0.5 h and then heated at 85 °C for 24 h under N_2. After which, the solution was concentrated and the resulting residue was dissolved in THF (5 mL) and added slowly into vigorously stirred

cold MeOH (0 °C, 50 mL). The resulting suspension was filtered by suction filtration to afford polymer **5-18** (0.80 g, 55% yield). Loading calcd by ^{1}H NMR: 0.780 mmol/g. ^{1}H NMR ($CDCl_3$): δ 8.75 (s, *CH* (byp), 1H), 7.11-6.61 (m, *ArH*, 98H), 5.31 (s, Ar*CH*$_2$ (byp), 4H), 5.14 (s, Ar*CH*$_2$ (p), 4H), 3.87 (s, CO_2*CH*$_3$ (byp), 4H), 3.67 (s, CO_2*CH*$_3$ (p), 6H), 3.38 (s, *CH*$_2$ (p), 3H), 2.88 (s, *CH*$_3$ (byp), 8H), 2.20 (s, *CH*$_3$ (p), 16H), 1.87-0.97 (m, 66H). IR (KBr, cm^{-1}): 3422.7, 3058.8, 3025.0, 2921.9, 2852.5, 1944.9, 1880.1, 1701.7, 1611.9, 1510.9, 1451.8, 1380.9, 1008.4, 820.1, 758.2, 698.3, 540.0.

5.4.5 Synthesis of polymer 5-19

Polymer **5-19** was prepared using the same procedure as described for the synthesis of **5-18** (62% yield). Loading calcd by ^{1}H NMR: 1.562 mmol/g. ^{1}H NMR ($CDCl_3$): δ 7.05-6.48 (m, *ArH*, 26H), 5.09 (s, Ar*CH*$_2$, 2H), 3.47 (s, CO*CH*$_2$CO, 2H), 2.21 (s, *CH*$_3$, 3H), 1.96-0.89 (m, 18H). IR (KBr, cm^{-1}): 3448.8, 3059.7, 3026.0, 2923.5, 2849.8, 1744.2, 1719.7, 1601.4, 1493.2, 1452.7, 1150.1, 1028.8, 759.2, 699.6, 540.5.

5.4.6 Synthesis of polymer 5-20

To polymer **5-19** (1.042 g, 1.6272 mmol) in THF (20 mL) and H_2O (4 mL) was added methyl 3-aminocrotonate (0.1873 g, 1.6272 mmol) and HCHO (37% solution, 0.122 mL, 1.6272 mmol). The mixture was heated under microwave irradiation at 100 °C for 20 min and then added slowly into vigorously stirred cold MeOH (0 °C, 200 mL). The resulting suspension was filtered by suction filtration to afford polymer **5-20** (1.17 g, 96% yield). Loading calcd by ^{1}H NMR: 0.925 mmol/g, loading calcd by elemental analysis: 0.908 mmol/g. ^{1}H NMR ($CDCl_3$): δ 8.80 (s, *CH* (byp), 1H), 7.07-6.49 (m, *ArH*, 420H), 5.27 (s, Ar*CH*$_2$ (byp), 9H), 5.10 (s, Ar*CH*$_2$ (p), 25H), 3.87 (s, CO_2*CH*$_3$ (byp), 4H), 3.65 (s, CO_2*CH*$_3$ (p), 29H), 3.35 (s,

CH_2 (p), 15H), 2.94 (s, *CH_3* (byp), 7H), 2.19 (s, *CH_3* (p), 69H), 1.82-0.94 (m, 318H). IR (KBr, cm^{-1}): 3468.9, 3409.6, 3082.3, 3059.2, 3025.5, 2922.8, 2849.6, 1736.02, 1716.55, 1601.8, 1493.2, 1452.4, 1271.2, 1184.2, 1114.0, 759.9, 699.3, 540.4.

5.4.7 General procedure for reduction of α,β-unsaturated aldehydes

To *trans*-4-nitrocinnamaldehyde (0.0354 g, 0.2 mmol) in CH_2Cl_2 (1.5 mL) was added polymer **5-20** (0.324 g, 0.3 mmol) and catalyst **5D**. This mixture was allowed to stir at rt for 4 h. After which, the mixture was filtered and washed with a mixture of EtOAc:hexane = 1:3 and filtered through silica gel. The filtrate was concentrated to afford **5-21a** as a pale yellow solid (0.032 g, 90% yield). ^{1}H NMR ($CDCl_3$): δ 9.77 (s, *CHO*, 1H), 8.04-8.02 (d, *J* = 8.7 Hz, *ArH*, 2H), 7.34-7.31 (d, *J* = 8.7 Hz, *ArH*, 2H), 3.03-2.98 (t, *J* = 7.2 Hz, *CH_2*CH_2CHO, 2H), 2.85-2.81 (m, CH_2*CH_2*CHO, 2H); ^{13}C NMR ($CDCl_3$): δ 200.2, 148.3, 146.1, 129.0, 123.3, 44.0, 27.4; Mass spectrum (EI) m/z 179.0 (M^+) Exact mass calcd for $C_9H_9NO_3$: m/z 179.0582; found 179.0581.

5.4.8 General procedure for reductive amination

To benzyl aldehyde (0.0203 mL, 0.2 mmol), aniline (0.0182 mL, 0.2 mmol) and polymer **5-20** (0.324 g, 0.3 mmol) in THF (3 mL) was added one drop of 1.5 M HCl. The mixture was allowed to stir at rt for 5 min. After which, the mixture was filtered and washed with a mixture of EtOAc:hexane = 1:5 and filtered through silica gel. The filtrate was then concentrated to afford **5-22a** (0.033 g, 90% yield). ^{1}H NMR ($CDCl_3$): δ 7.27-6.51 (m, *ArH*, 10H), 4.21 (s, *CH_2*, 2H), 3.66 (s, *NH*, 1H); ^{13}C NMR ($CDCl_3$): δ 148.0, 139.4, 129.2, 128.6, 127.5, 127.2, 117.6, 112.9, 48.2; Mass spectrum (EI) m/z 183.0 (M^+) Exact mass calcd for $C_{13}H_{13}N$: m/z 183.1048; found 183.1047.

5.4.9 General procedure for aromatization of benzoquinone

To 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.0454 g, 0.2 mmol) in THF (2 mL) was added polymer **5-20** (0.324 g, 0.3 mmol). The mixture was allowed to stir at rt for 5 min. After which, it was added into cold MeOH (20 mL), filtered and concentrated to afford **5-23** as a yellow solid (0.0455 g, 99% yield). ^{13}C NMR ($CDCl_3$): δ 150.8, 129.2, 113.7, 101.7; Mass spectrum (EI) m/z 227.8 (M^+) Exact mass calcd for $C_8H_2Cl_2N_2O_2$: m/z 227.9493; found 227.9491.

5-21b: 3-Phenylpropanal. ^{1}H NMR ($CDCl_3$): δ 9.74 (s, *CHO*, 1H), 7.24-7.10 (m, *ArH*, 5H), 2.91-2.86 (t, *J* = 7.5 Hz, CH_2CH_2CHO, 2H), 2.72-2.67 (m, CH_2CH_2CHO, 2H); ^{13}C NMR ($CDCl_3$): δ 201.5, 140.3, 128.6, 128.2, 126.3, 45.2, 28.1; Mass spectrum (EI) m/z 133.9 (M^+) Exact mass calcd for $C_9H_{10}O$: m/z 134.0732; found 134.0728.

5-21c: 3-(4-Methoxyphenyl)propanal. ^{1}H NMR ($CDCl_3$): δ 9.80 (s, *CHO*, 1H), 7.12-7.10 (d, *J* = 8.7 Hz, *ArH*, 2H), 6.85-6.82 (d, *J* = 8.7 Hz, *ArH*, 2H), 3.78 (s, OCH_3, 3H), 2.93-2.88 (t, *J* = 7.5 Hz, CH_2CH_2CHO, 2H), 2.76-2.71 (m, CH_2CH_2CHO, 2H); ^{13}C NMR ($CDCl_3$): δ 201.7, 158.1, 132.3 129.2, 114.0, 55.2, 45.5, 27.2; Mass spectrum (EI) m/z 163.9 (M^+) Exact mass calcd for $C_{10}H_{12}O_2$: m/z 164.0837; found 164.0832.

5-22b: *N*-(4-Methoxybenzyl)benzenamine. ^{1}H NMR ($CDCl_3$): δ 7.32-6.66 (m, *ArH*, 9H), 4.27 (s, CH_2, 2H), 3.82 (s, OCH_3, 3H); ^{13}C NMR ($CDCl_3$): δ 158.9, 147.9, 131.2, 129.2, 128.8, 117.7, 114.0, 113.0, 55.3, 47.9; Mass spectrum (EI) m/z 213.0 (M^+) Exact mass calcd for $C_{14}H_{15}NO$: m/z 213.1154; found 213.1156.

5-22c: *N*-(4-Nitrobenzyl)benzenamine. ^{1}H NMR ($CDCl_3$): δ 8.20-6.59 (m, *ArH*, 9H), 4.48 (s, CH_2, 2H); ^{13}C NMR ($CDCl_3$): δ 147.3, 147.2, 147.1, 129.4, 127.7, 123.8, 118.4, 113.1, 47.7;

Mass spectrum (EI) m/z 228.0 (M^+) Exact mass calcd for $C_{13}H_{12}N_2O_2$: m/z 228.0899; found 228.0900.

5-22d: *N*-(2-Pyridinylmethyl)benzenamine. ^{1}H NMR ($CDCl_3$): δ 8.60-6.66 (m, *ArH*, 9H), 4.48 (s, CH_2, 2H), 3.82 (s, *NH*, 1H); ^{13}C NMR ($CDCl_3$): δ 158.4, 148.8, 147.8, 136.9, 129.2, 122.2, 121.7, 117.6, 113.0, 49.1; Mass spectrum (EI) m/z 183.9 (M^+) Exact mass calcd for $C_{12}H_{12}N_2$: m/z 184.1000; found 184.0994.

5-22e: *N*-(2-Furanylmethyl)benzenamine. ^{1}H NMR ($CDCl_3$): δ 7.39 (s, *ArH*, 1H), 7.39-6.26 (m, *ArH*, 7H), 4.34 (s, CH_2, 2H), 3.73 (s, *NH*, 1H); ^{13}C NMR ($CDCl_3$): δ 152.6, 147.5, 141.9, 129.2, 118.1, 113.2, 110.3, 107.0, 41.5; Mass spectrum (EI) m/z 173.0 (M^+) Exact mass calcd for $C_{11}H_{11}NO$: m/z 173.0841; found 173.0835.

5-22f: *N*-(2-Thiophenylmethyl)benzenamine. ^{1}H NMR ($CDCl_3$): δ 7.26-6.70 (m, *ArH*, 8H), 4.54 (s, CH_2, 2H), 3.76 (s, *NH*, 1H); ^{13}C NMR ($CDCl_3$): δ 147.4, 142.8, 129.2, 126.8, 125.1, 124.6, 118.2, 113.3, 43.5; Mass spectrum (EI) m/z 189.0 (M^+) Exact mass calcd for $C_{11}H_{11}NS$: m/z 189.0612; found 189.0614.

5-22g: *N*-Benzyl-4-chlorobenzenamine. ^{1}H NMR ($CDCl_3$): δ 7.36-6.56 (m, *ArH*, 9H), 4.31 (s, CH_2, 2H); ^{13}C NMR ($CDCl_3$): δ 146.4, 138.7, 129.1, 128.7, 127.5, 127.4, 122.4, 114.1, 48.5; Mass spectrum (EI) m/z 217.0 (M^+) Exact mass calcd for $C_{13}H_{12}ClN$: m/z 217.0658; found 217.0655.

5-22h: *N*-Benzyl-4-nitrobenzenamine. ^{1}H NMR ($CDCl_3$): δ 8.09-8.06 (d, J = 9.1 Hz, *ArH*, 2H), 7.40-6.31 (m, *ArH*, 5H), 6.59-6.56 (d, J = 9.1 Hz, *ArH*, 2H), 4.43 (s, CH_2, 2H); ^{13}C NMR ($CDCl_3$): δ 153.0, 138.4, 137.3, 128.9, 127.8, 127.3, 126.4, 111.4, 47.7; Mass spectrum (EI) m/z 228.0 (M^+) Exact mass calcd for $C_{13}H_{12}N_2O_2$: m/z 228.0899; found 228.0898.

5-22i: *N*-Benzyl-4-tert-butylbenzenamine. ^{1}H NMR ($CDCl_3$): δ 7.34-6.51 (m, *ArH*, 9H), 4.22 (s, CH_2, 2H), 1.19 (s, CH_3, 9H); ^{13}C NMR ($CDCl_3$): δ 145.6, 140.5, 139.5, 128.6, 127.6, 127.2, 126.0, 112.7, 48.8, 43.5, 31.5; Mass spectrum (EI) m/z 239.1 (M^+) Exact mass calcd for $C_{17}H_{21}N$: m/z 239.1674; found 239.1673.

5.5 References

[1] (a) Helfferich, F. G. *Ion Exchange*. McGraw-Hill: New York, 1962. (b) Hodge, P.; Sherrington, D. C. *Polymer-Supported Reactions in Organic Synthesis*. John Wiley: Chichester, 1980. (c) Hodge, P.; Sherrington, D. C. *Syntheses and Separations Using Functional Polymers*. John Wiley: Chichester, 1988. (d) Akelah, A.; Sherrington, D. C. *Polymer* **1983**, *24*, 1369-1386. (e) Gladysz, J. A. *Chem. Rev.* **2002**, *102*, 3215-3216.

[2] Hodge, P. *Ind. Eng. Chem. Res.* **2005**, *44,* 8542-8553.

[3] McNamara, C. A.; Dixon, M. J.; Bradley, M. *Chem. Rev.* **2002**, *102,* 3275-3300.

[4] Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102,* 3217-3274.

[5] Fraile, J. M; Mayoral, J. A; Royo, A. J.; Salvador, R. V.; Altava, B.; Luis, S. V.; Burguete, M. I. *Tetrahedron* **1996**, *52*, 9853-9862.

[6] Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc.* **1982**, *104*, 6112-6114.

[7] Trost, B. M.; Keinan, E. *J. Am. Chem. Soc.* **1978**, *100*, 7779-7781.

[8] Yu, H-B.; Zheng, X-F.; Lin, Z-M.; Hu, Q-S.; Huang, W-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 8149-8155.

[9] Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002,** *102,* 3325-3344.

[10] (a) Harrison, C. R.; Hodge, P.; Hunt, B. J.; Khoshdel, E.; Richardson, G. *J. Org. Chem.* **1983**, *48*, 3721-3728. (b) Charette, A. B.; Boezio, A. A.; Janes, M. K. *Org. Lett.* **2000**, *2*, 3777-3779. (c) Bergbreiter, D. E.; Blanton, J. R. *J. Chem. Soc., Chem. Commun.* **1985**, 337-338. (d) Wentworth, P. Jr.; Vandersteen, A. M.; Janda, K. D. *Chem.Commun.* **1997**, 759-760. (e) Holletz, T.; Cech, D. *Synthesis.* **1994**, 789-791.

[11] Harris, J. M.; Liu, Y.; Chai, S.; Andrews, M. D.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2407-2409.

[12] Hallensleben, M. L. *J. Polym. Sci., Polym. Symp.* **1974**, *47*, 1-9.

[13] Avny, Y.; Marom, G.; Zilkha, A. *Eur. Polym. J.* **1971**, *7*, 1037.

[14] Smith, T. W.; Cheatham, R. A. *Macromolecules* **1980**, *13*, 1203-1207.

[15] (a) Bayer, E.; Schurig, V. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 493-494. (b) Fan, Q. H.; Deng, G. J.; Lin, C. C.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1241-1247.

[16] Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, *31*, 3003-3006.

[17] Reger, T. S.; Janda, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 6929-6934.

[18] (a) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546-554. (b) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489-510. (c) Wentworth Jr., P.; Janda, K. D. *Chem. Commun.* **1999**, 1917-1924. (d) Bergbreiter, D. E. *Med Res. Rev.* **1999**, *19*, 439-450.

[19] Zhao, X.; Metz, W. A.; Sieber, F.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 8433-8436.

[20] Mutter, M.; Mutter, H.; Uhmann, R.; Bayer, E. *Biopolymers* **1976**, *15*, 917-927.

[21] Hantzsch, A. *Jusfus Liebigs Ann. Chem.* **1882**, *215*, 1-82.

[22] (a) Bruice, T. C.; Benkovic, S. J. *Bioorganic Mechanisms*. Vol 2, Benjamin, W. A.: New York, 1966. (b) Florkin, M.; Stotz, E. H. *Comprehensive Biochemistry*. Vol 14, Elsevier: Amsterdam, 1966.

[23] (a) Murakami, Y.; Kikuchi, J. I.; Hisaeda, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 721-758. (b) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223-243. (c) Eisner, U.;

Kuthan, J. *Chem. Rev.* **1972**, *72*, 1-42. (d) Carlson, B. W.; Miller, L. L. *J. Am. Chem. Soc.* **1983**, *105*, 7453-7454. (e) Sinha, A.; Bruice, T. C. *J. Am. Chem. Soc.* **1984**, *106*, 7291-7292.

[24] (a) Tanner, D. D.; Singh, H. K.; Kharrat, A.; Stein, A. R. *J. Org. Chem.* **1987**, *52*, 2142-2146. (b) Tanner, D. D.; Stein, A. R. *J. Org. Chem.* **1988**, *53*, 1642-1646. (c) Fukuzumi, S.; Mochizuki, S.; Tanaka, T. *J. Am. Chem. Soc.* **1989**, *111*, 1497-1499.

[25] (a) Fukuzumi, S.; Ish-ikama, M.; Tanaka, T. *Tetrahedron* **1984**, *42*, 1021-1034. (b) Gelbard, G.; Lin, J.; Roques, N. *J. Org. Chem.* **1992**, *57*, 1789-1793. (c) Kanomata, N.; Suzuki, M.; Yoshida, M.; Nakata, T. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1410-1412.

[26] (a) Braude, E. A.; Hannah, J.; Linstead, R. *J. Chem. Soc.* **1960**, 3249-3257. (b) Garden, S. J.; Garden, S. J.; Guimaraes, C. R. W.; Correa, M. B.; Oliveira, C. A. F.; Cunha Pinto, A.; Alencastro, R. B. *J. Org. Chem.* **2003**, *68*, 8815-8822. (d) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 6660-6662.

[27] (a) Zehani, S.; Lin, J.; Gelbard, G. *Tetrahedron* **1989**, *45*, 733- 740. (b) Burgess, V. A.; Davies, S. G.; Skerlj, R. T.; Whittaker, M. *Tetrahedron: Asymmetry* **1992**, *3*, 871-901. (c) Kanomata, N.; Nakata, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1207-1211. (d) Obika, S.; Nishiyama, T.; Tatematsu, S.; Miyashita, K.; Iwata, C.; Imanishi, T. *Tetrahedron* **1997**, *53*, 593-602. (e) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 7424-7427. (f) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036-15037. (g) Rueping, M.;

Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781-3783.

[28] (a) Steevens, J. B.; Pandit, U. K. *Tetrahedron* **1983**, *39*, 1395-1400. (b) Fujii, M.; Aida, T.; Yoshihara, M.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3845-3847. (c) Itoh, T.; Nagata, A.; Kurihara, A.; Miyazaki, M.; Ohsawa, A. *Tetrahedron Lett.* **2002**, *43*, 3105-3108. (d) Itoh, T.; Nagata, K.; Miyazaki, M.; Ishikawa, H.; Kurihara, A.; Ohsawa, A. *Tetrahedron* **2004**, *60*, 6649-6655. (e) Menche, D.; Hassfeld, J.; Li, J.; Menche, G.; Ritter, A.; Rudolph, S. *Org. Lett.* **2006**, *8*, 741-744.

[29] Janis, R. A.; Triggle, D. J. *J. Med. Chem*. **1983**, *26,* 775-785.

[30] (a) Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 269-290. (b) Gordeev, M. F.; Patel, D. V.; Gordon, E. M. *J. Org. Chem*. **1996**, *61*, 924-928. (c) Coburn, R. A.; Wierzba, M.; Suto, M. J.; Solo, A. J.; Triggle, A. M.; Triggle, D. J. *J. Med. Chem*. **1988**, *31*, 2103-2107. (d) Godfraind, T.; Miller, R.; Wibo, M. *Pharmacol. Rev.* **1986**, *38*, 321-416.

[31] (a) Sabitha, G.; Reddy, G.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett.* **2003**, *44*, 4129-4133. (b) Watanabe, Y.; Shiota, K.; Hoshiko, T.; Ozoki, S. *Synthesis* **1983**, *9*, 761-762. (c) Anniyappan, M.; Muralidharan, D.; Perumal, P. T. *Synth. Commun.* **2002**, *32*, 659-663. (d) Ohberg, L.; Westman, J. *Synlett*. **2001**, *8*, 1296-1298. (e) Salehi1, H.; Guo, Q. *Synth. Commun.* **2004**, *34*, 4349-4357. (f) Torchy, S.; Cordonnier, G.; Barbry, D.; Vanden Eynde, J-J. *Molecules* **2002**, *7*, 528-533. (g) Kosower, E. M.; Sorensen, T. S. *J. Org. Chem.* **1962**, *27*, 3764-3771. (h) Yamada, S.; Kikugawa, Y. *Chem. Ind. (London)*. **1966**, *52*, 2169-2170.

Appendix A

Table 1. Crystal data and structure refinement for **2-1-10**.

Identification code	**2-1-10**	
Empirical formula	$C_{15}\ H_{19}\ N_3\ O_4$	
Formula weight	305.33	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.4643(6) Å	α = 87.911(2)°.
	b = 9.8277(9) Å	β = 85.389(2)°.
	c = 11.9782(11) Å	γ = 81.272(2)°.
Volume	749.49(12) $Å^3$	
Z	2	
Density (calculated)	1.353 Mg/m^3	
Absorption coefficient	0.100 mm^{-1}	
F(000)	324	
Crystal size	0.68 x 0.57 x 0.24 mm^3	
Theta range for data collection	1.71 to 30.03°.	
Index ranges	-9<=h<=9, -13<=k<=13, -16<=l<=16	
Reflections collected	11734	
Independent reflections	4347 [R(int) = 0.0249]	
Completeness to theta = 30.03°	99.2 %	
Absorption correction	None	
Max. and min. transmission	0.9763 and 0.9357	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4347 / 0 / 203	
Goodness-of-fit on F^2	1.038	
Final R indices [I>2sigma(I)]	R1 = 0.0521, wR2 = 0.1375	
R indices (all data)	R1 = 0.0619, wR2 = 0.1452	
Largest diff. peak and hole	0.429 and -0.234 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2-1-10**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	3579(1)	9556(1)	1391(1)	31(1)
O(4)	8174(2)	6244(1)	7125(1)	33(1)
N(1)	8288(2)	7098(1)	1761(1)	26(1)
O(2)	6196(2)	9831(1)	2463(1)	42(1)
C(8)	9191(2)	7173(1)	3729(1)	25(1)
N(2)	7038(2)	5694(1)	657(1)	28(1)
O(3)	11850(2)	8400(1)	4114(1)	37(1)
C(4)	5428(2)	9131(1)	1841(1)	28(1)
C(9)	10369(2)	7630(1)	4536(1)	25(1)
C(10)	10000(2)	7307(1)	5663(1)	28(1)
C(3)	5606(2)	6869(1)	783(1)	24(1)
N(3)	3802(2)	7024(1)	253(1)	34(1)
C(2)	6324(2)	7770(1)	1481(1)	24(1)
C(13)	7652(2)	6398(1)	4088(1)	32(1)
C(7)	9710(2)	7545(1)	2516(1)	28(1)
C(12)	7240(2)	6068(1)	5218(1)	33(1)
C(11)	8422(2)	6523(1)	5996(1)	26(1)
C(1)	8604(2)	5888(1)	1258(1)	29(1)
C(5)	2593(2)	10936(1)	1697(1)	39(1)
C(15)	6309(2)	5727(2)	7531(1)	40(1)
C(6)	639(2)	11288(2)	1097(1)	40(1)
C(14)	12977(2)	9011(2)	4887(1)	40(1)

Table 3. Bond lengths [Å] and angles [°] for **2-1-10**.

O(1)-C(4)	1.3525(15)
O(1)-C(5)	1.4552(15)
O(4)-C(11)	1.3720(14)
O(4)-C(15)	1.4218(16)
N(1)-C(1)	1.3340(16)
N(1)-C(2)	1.3993(15)
N(1)-C(7)	1.4629(14)
O(2)-C(4)	1.2139(15)
C(8)-C(13)	1.3757(16)
C(8)-C(9)	1.4044(15)
C(8)-C(7)	1.5092(16)
N(2)-C(1)	1.3280(15)
N(2)-C(3)	1.3704(15)
O(3)-C(9)	1.3633(14)
O(3)-C(14)	1.4256(15)
C(4)-C(2)	1.4412(17)
C(9)-C(10)	1.3851(16)
C(10)-C(11)	1.3944(17)
C(3)-N(3)	1.3572(15)
C(3)-C(2)	1.3937(15)
C(13)-C(12)	1.3939(18)
C(12)-C(11)	1.3784(16)
C(5)-C(6)	1.492(2)
C(4)-O(1)-C(5)	114.48(10)
C(11)-O(4)-C(15)	116.96(10)
C(1)-N(1)-C(2)	106.72(10)
C(1)-N(1)-C(7)	124.68(10)
C(2)-N(1)-C(7)	128.46(10)
C(13)-C(8)-C(9)	118.11(10)
C(13)-C(8)-C(7)	123.93(10)
C(9)-C(8)-C(7)	117.96(10)
C(1)-N(2)-C(3)	104.93(10)
C(9)-O(3)-C(14)	117.91(10)
O(2)-C(4)-O(1)	123.07(12)
O(2)-C(4)-C(2)	125.81(12)

O(1)-C(4)-C(2)	111.12(10)
O(3)-C(9)-C(10)	124.47(10)
O(3)-C(9)-C(8)	114.51(10)
C(10)-C(9)-C(8)	121.01(11)
C(9)-C(10)-C(11)	119.24(11)
N(3)-C(3)-N(2)	120.44(10)
N(3)-C(3)-C(2)	129.37(11)
N(2)-C(3)-C(2)	110.18(10)
C(3)-C(2)-N(1)	104.78(10)
C(3)-C(2)-C(4)	131.29(11)
N(1)-C(2)-C(4)	123.87(10)
C(8)-C(13)-C(12)	121.93(11)
N(1)-C(7)-C(8)	113.06(9)
C(11)-C(12)-C(13)	119.00(11)
O(4)-C(11)-C(12)	123.98(11)
O(4)-C(11)-C(10)	115.31(10)
C(12)-C(11)-C(10)	120.71(11)
N(2)-C(1)-N(1)	113.37(11)
O(1)-C(5)-C(6)	108.44(11)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **2-1-10**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	31(1)	27(1)	36(1)	-8(1)	-6(1)	-3(1)
O(4)	39(1)	39(1)	23(1)	0(1)	-4(1)	-10(1)
N(1)	26(1)	30(1)	22(1)	-3(1)	-5(1)	-6(1)
O(2)	43(1)	38(1)	47(1)	-17(1)	-12(1)	-7(1)
C(8)	26(1)	26(1)	23(1)	-3(1)	-5(1)	-6(1)
N(2)	28(1)	30(1)	28(1)	-7(1)	-6(1)	-2(1)
O(3)	38(1)	51(1)	30(1)	-3(1)	-6(1)	-26(1)
C(4)	30(1)	29(1)	27(1)	-4(1)	0(1)	-8(1)
C(9)	24(1)	26(1)	27(1)	-4(1)	-5(1)	-6(1)
C(10)	29(1)	30(1)	25(1)	-6(1)	-7(1)	-6(1)
C(3)	25(1)	27(1)	21(1)	-2(1)	-2(1)	-5(1)
N(3)	30(1)	32(1)	41(1)	-12(1)	-13(1)	-1(1)
C(2)	25(1)	28(1)	21(1)	-2(1)	-2(1)	-6(1)
C(13)	36(1)	38(1)	26(1)	-3(1)	-8(1)	-17(1)
C(7)	27(1)	37(1)	24(1)	-1(1)	-6(1)	-12(1)
C(12)	37(1)	37(1)	29(1)	0(1)	-5(1)	-18(1)
C(11)	31(1)	25(1)	23(1)	-2(1)	-3(1)	-4(1)
C(1)	28(1)	32(1)	27(1)	-4(1)	-5(1)	-2(1)
C(5)	41(1)	29(1)	45(1)	-10(1)	-6(1)	1(1)
C(15)	42(1)	48(1)	31(1)	4(1)	0(1)	-12(1)
C(6)	40(1)	32(1)	46(1)	1(1)	-4(1)	-1(1)
C(14)	40(1)	49(1)	39(1)	-4(1)	-13(1)	-22(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **2-1-10**.

	x	y	z	U(eq)
H(10)	10804	7612	6196	33
H(3A)	3549	6376	-169	41
H(3B)	2899	7772	337	41
H(13)	6854	6082	3557	39
H(7A)	9649	8546	2437	34
H(7B)	11150	7122	2293	34
H(12)	6173	5543	5446	39
H(1)	9815	5236	1322	35
H(5A)	3554	11600	1486	47
H(5B)	2251	10972	2509	47
H(15A)	5097	6367	7323	60
H(15B)	6269	5622	8340	60
H(15C)	6287	4841	7205	60
H(6A)	982	11207	297	60
H(6B)	2	12226	1260	60
H(6C)	-339	10662	1345	60
H(14A)	11994	9566	5404	60
H(14B)	13888	9590	4482	60
H(14C)	13817	8294	5302	60

Table 1. Crystal data and structure refinement for **2-1-7h**.

Identification code	**2-1-7h**	
Empirical formula	$C_{11}\ H_{10}\ N_4\ O_2$	
Formula weight	230.23	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 17.503(3) Å	α = 90°.
	b = 8.0041(12) Å	β = 95.742(4)°.
	c = 7.6603(12) Å	γ = 90°.
Volume	1067.8(3) $Å^3$	
Z	4	
Density (calculated)	1.432 Mg/m^3	
Absorption coefficient	0.103 mm^{-1}	
F(000)	480	
Crystal size	0.468 x 0.312 x 0.26 mm^3	
Theta range for data collection	2.34 to 27.49°.	
Index ranges	-22<=h<=21, -10<=k<=10, -6<=l<=9	
Reflections collected	3696	
Independent reflections	1232 [R(int) = 0.0211]	
Completeness to theta = 27.49°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1232 / 29 / 105	
Goodness-of-fit on F^2	1.167	
Final R indices [I>2sigma(I)]	R1 = 0.1732, wR2 = 0.3154	
R indices (all data)	R1 = 0.1777, wR2 = 0.3167	
Extinction coefficient	0.0060(13)	
Largest diff. peak and hole	0.701 and -0.660 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2-1-7h**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5000	3012(15)	2500	42(2)
C(2)	4393(4)	378(9)	1581(9)	35(2)
C(3)	5000	-466(12)	2500	36(2)
C(4)	4059(9)	-2058(19)	961(19)	41(4)
C(5)	3807(4)	3020(10)	536(9)	40(2)
C(6)	3250(20)	3480(50)	1750(50)	78(16)
C(7)	3195(11)	3650(30)	1600(30)	30(5)
C(8)	2806(12)	4320(30)	2380(30)	59(6)
C(9)	2854(19)	3690(50)	3090(30)	126(13)
N(1)	4729(8)	-2096(14)	2010(18)	43(3)
N(2)	3908(10)	-721(19)	810(20)	36(2)
N(3)	4426(3)	2110(7)	1570(8)	32(1)
O(1)	5000	4517(8)	2500	42(2)
O(2)	3816(8)	-329(15)	693(19)	36(2)

Table 3. Bond lengths [Å] and angles [°] for **2-1-7h**.

C(1)-O(1)	1.205(13)
C(1)-N(3)#1	1.376(8)
C(1)-N(3)	1.376(8)
C(2)-O(2)	1.290(17)
C(2)-N(2)	1.32(2)
C(2)-N(3)	1.387(9)
C(2)-C(3)	1.389(9)
C(3)-C(2)#1	1.389(9)
C(3)-N(1)#1	1.426(13)
C(3)-N(1)	1.426(13)
C(4)-N(2)	1.11(2)
C(4)-N(1)	1.35(2)
C(4)-O(2)	1.456(19)
C(5)-C(6)	1.466(10)
C(5)-N(3)	1.469(9)
C(5)-C(7)	1.500(9)
C(6)-C(8)	1.162(10)
C(7)-C(9)	1.338(10)
N(1)-N(1)#1	1.15(3)
O(1)-C(1)-N(3)#1	121.6(5)
O(1)-C(1)-N(3)	121.6(5)
N(3)#1-C(1)-N(3)	116.7(10)
O(2)-C(2)-N(2)	15.8(8)
O(2)-C(2)-N(3)	117.8(8)
N(2)-C(2)-N(3)	133.5(9)
O(2)-C(2)-C(3)	124.9(8)
N(2)-C(2)-C(3)	109.1(8)
N(3)-C(2)-C(3)	117.3(6)
C(2)#1-C(3)-C(2)	121.8(9)
C(2)#1-C(3)-N(1)#1	95.4(6)
C(2)-C(3)-N(1)#1	142.7(8)
C(2)#1-C(3)-N(1)	142.7(8)
C(2)-C(3)-N(1)	95.4(6)
N(1)#1-C(3)-N(1)	47.5(11)
N(2)-C(4)-N(1)	105.6(16)

N(2)-C(4)-O(2)	3.6(16)
N(1)-C(4)-O(2)	109.2(12)
C(6)-C(5)-N(3)	106.7(17)
C(6)-C(5)-C(7)	7(2)
N(3)-C(5)-C(7)	113.7(12)
C(8)-C(6)-C(5)	157(4)
C(9)-C(7)-C(5)	151(3)
N(1)#1-N(1)-C(4)	176(2)
N(1)#1-N(1)-C(3)	66.2(6)
C(4)-N(1)-C(3)	112.4(11)
C(4)-N(2)-C(2)	117.5(17)
C(1)-N(3)-C(2)	123.3(7)
C(1)-N(3)-C(5)	118.7(6)
C(2)-N(3)-C(5)	118.0(6)
C(2)-O(2)-C(4)	98.1(10)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **2-1-7h**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

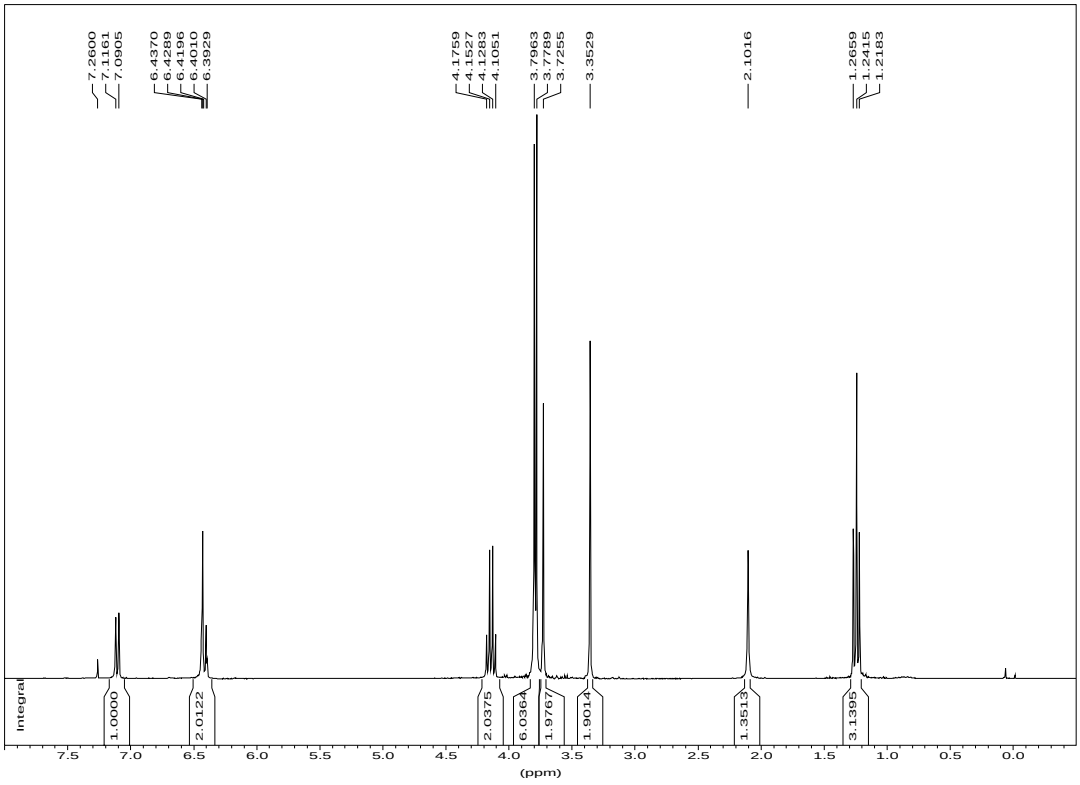
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	30(5)	49(6)	47(6)	0	6(4)	0
C(2)	31(3)	40(4)	36(4)	-17(3)	10(3)	-10(3)
C(3)	40(3)	17(4)	51(3)	0	11(2)	0
C(4)	58(9)	35(7)	34(7)	-17(6)	21(6)	-27(7)
C(5)	38(4)	42(4)	40(4)	0(3)	2(3)	1(3)
C(6)	72(18)	77(18)	83(18)	1(9)	1(9)	7(9)
C(7)	6(6)	26(8)	56(11)	0(7)	0(6)	8(5)
C(8)	64(11)	62(11)	48(10)	-25(9)	-10(8)	26(9)
C(9)	130(20)	160(20)	100(20)	15(18)	17(16)	-95(19)
N(1)	56(8)	19(5)	55(8)	-3(5)	11(6)	-5(5)
N(2)	40(3)	17(4)	51(3)	0	11(2)	0
N(3)	30(3)	30(3)	38(3)	-11(2)	6(2)	-5(2)
O(1)	45(4)	16(3)	64(5)	0	-4(3)	0
O(2)	40(3)	17(4)	51(3)	0	11(2)	0

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **2-1-7h**.

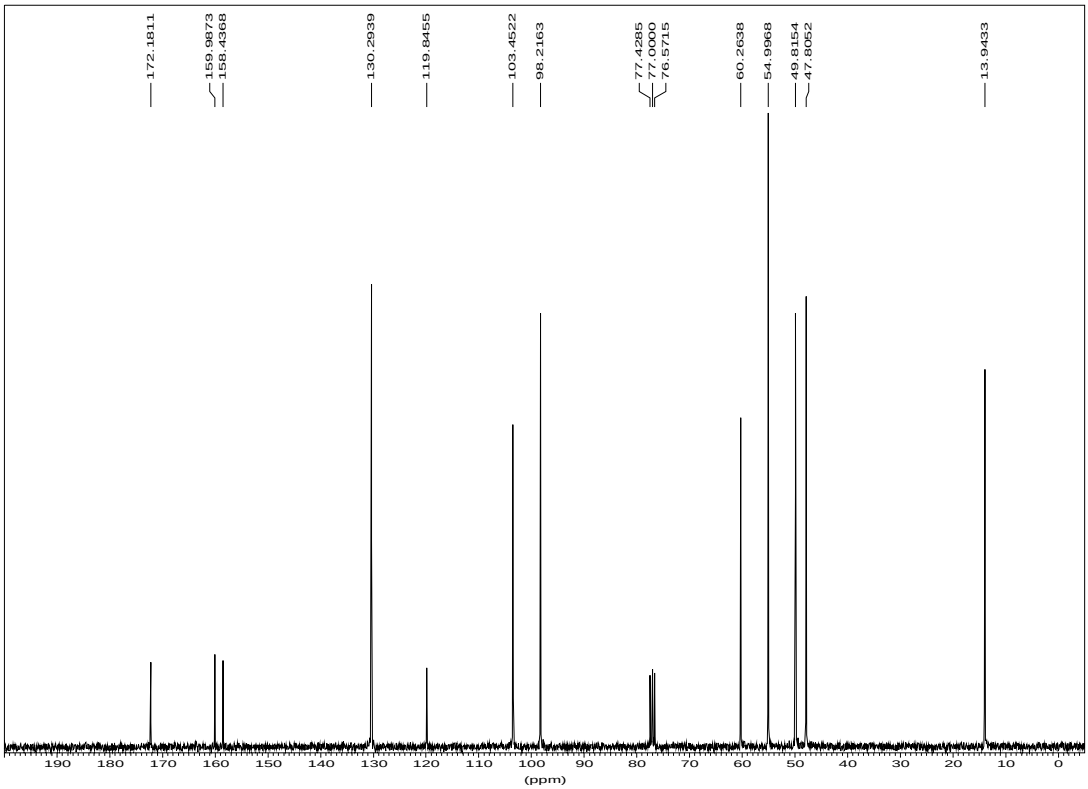
	x	y	z	U(eq)
H(7)	3781	-2975	465	50
H(5A)	4011	4021	10	48
H(5B)	3567	2309	-407	48
H(6A)	2908	4404	852	36
H(8)	2451	4997	2892	71
H(9A)	3045	3023	4047	152
H(9B)	2423	4373	3175	152
H(1N)	5000	-2970(40)	2500	80

Appendix B

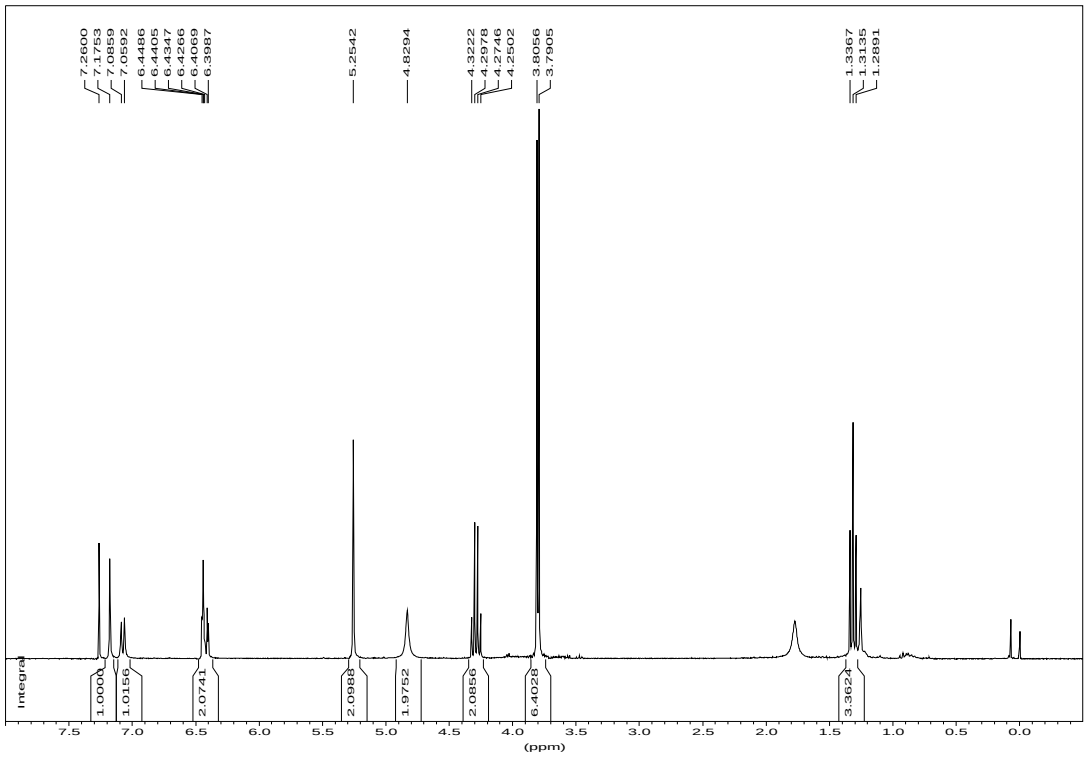
^{1}H NMR of **2-1-8**



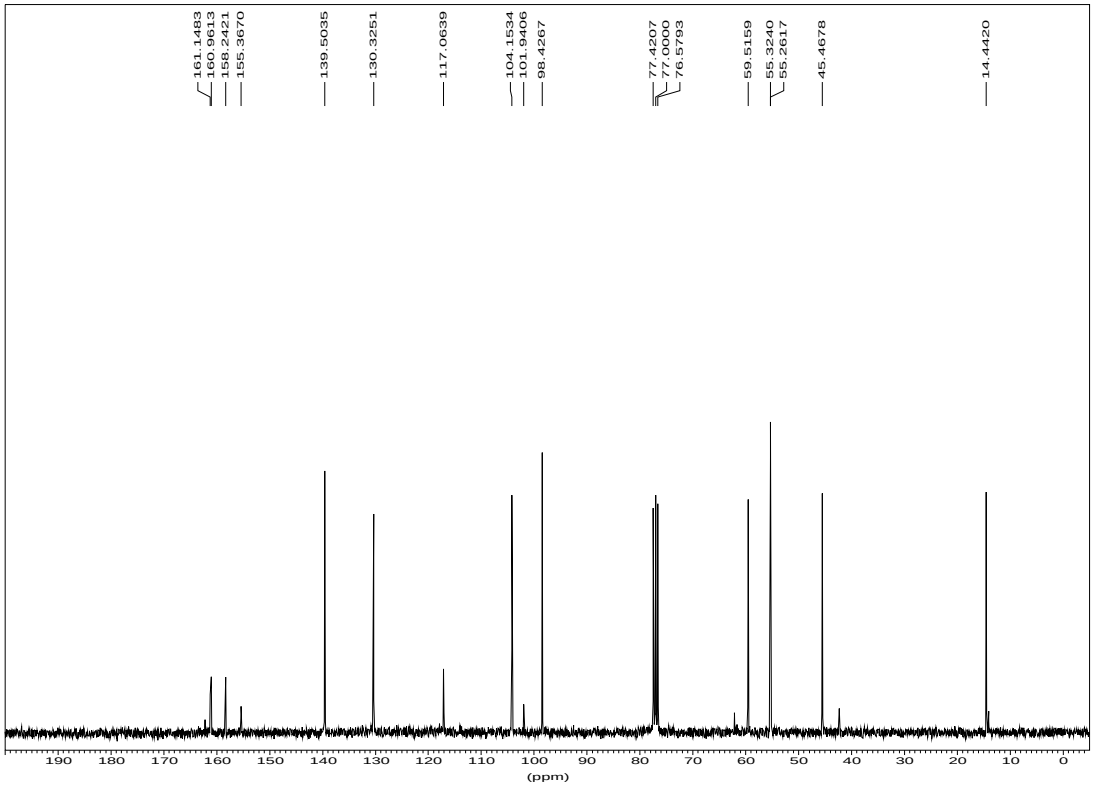
^{13}C NMR of **2-1-8**



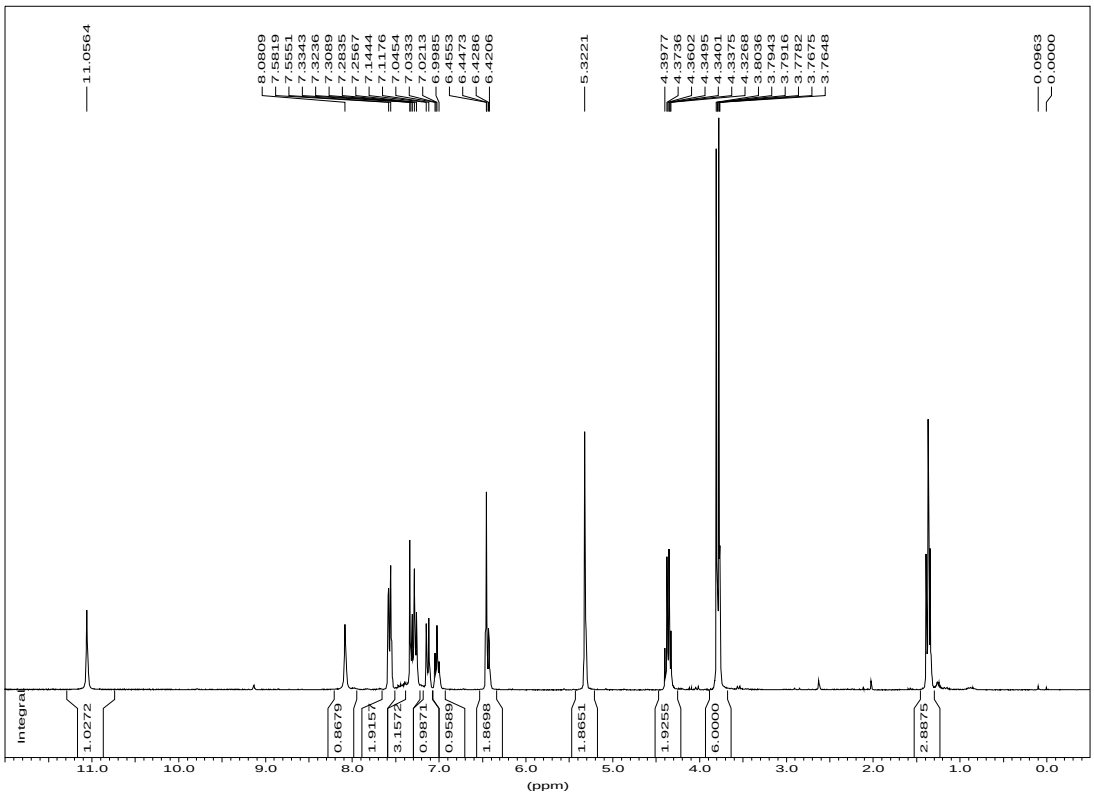
^{1}H NMR of **2-1-10**



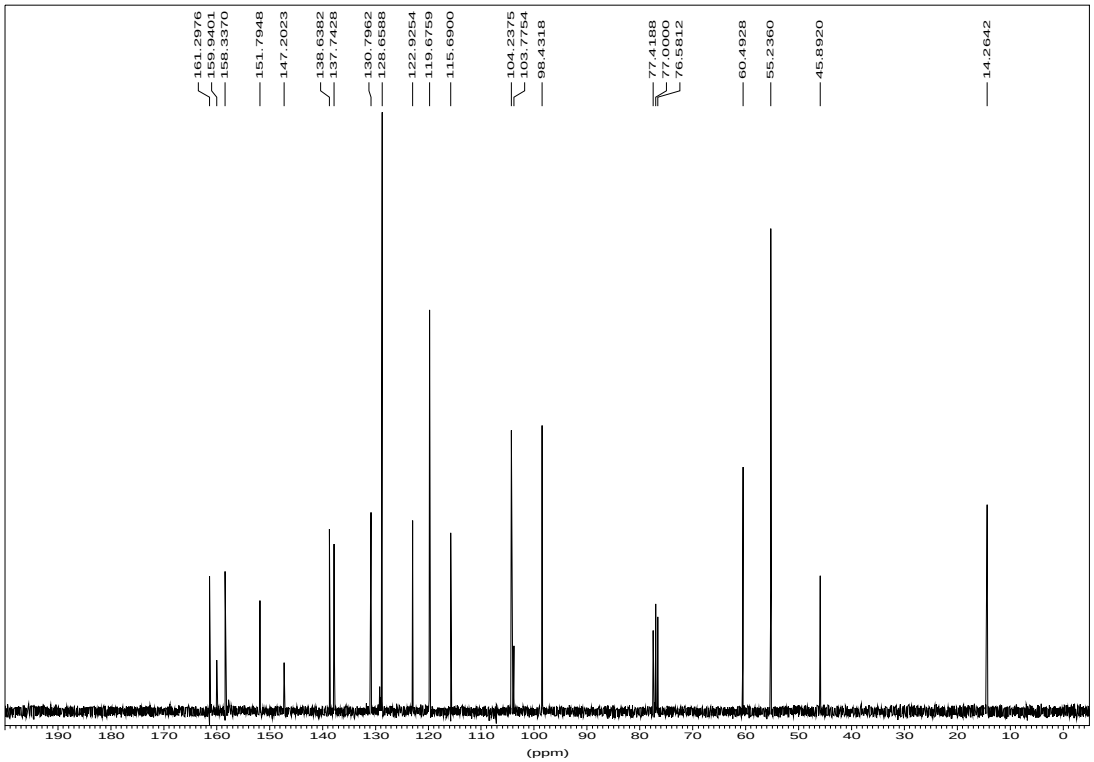
^{13}C NMR of **2-1-10**



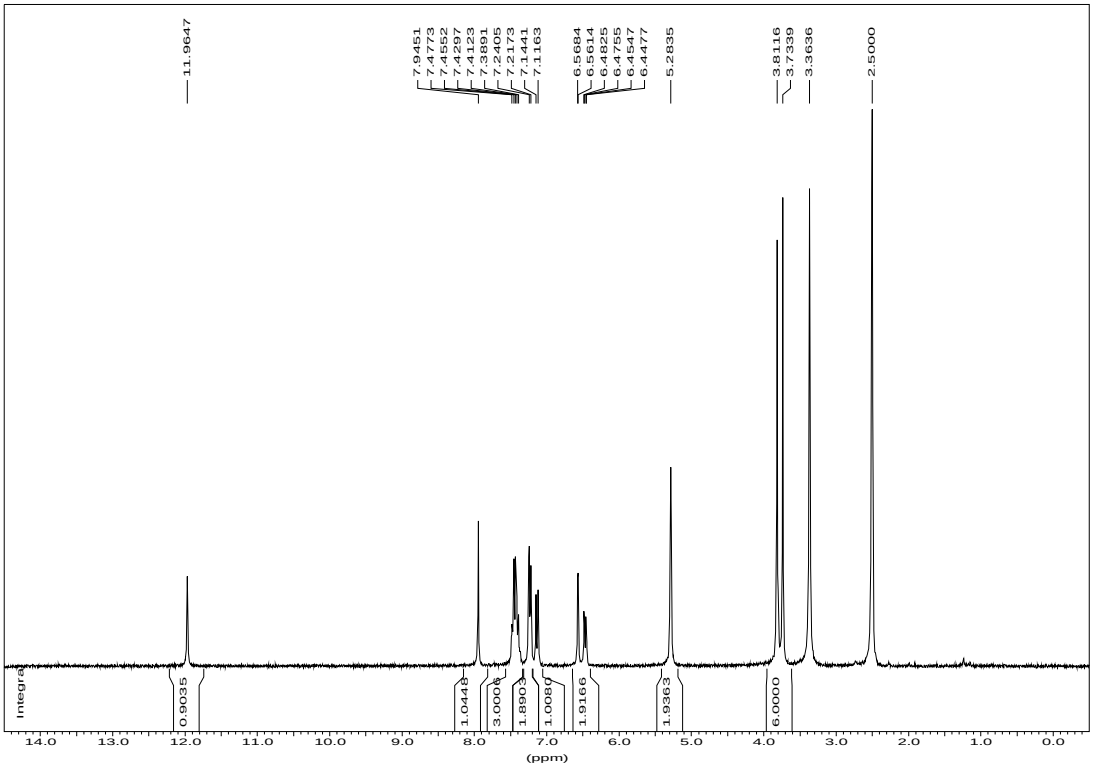
^{1}H NMR of **2-1-11**



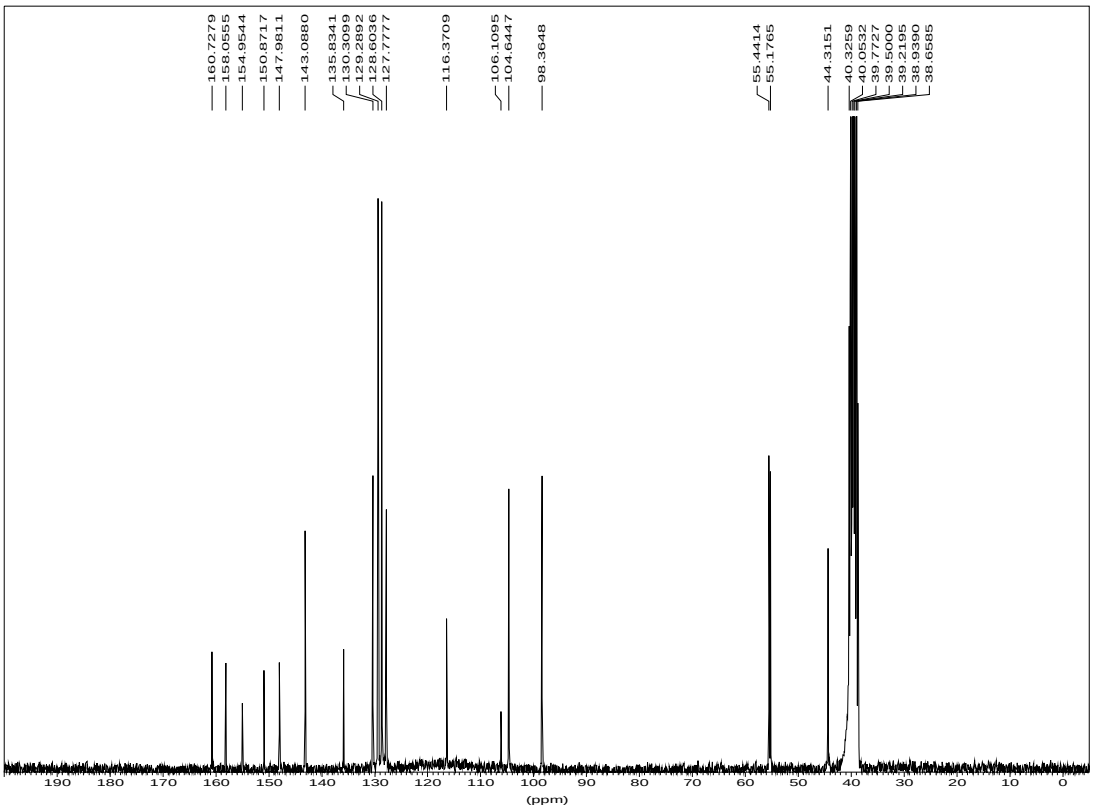
^{13}C NMR of **2-1-11**



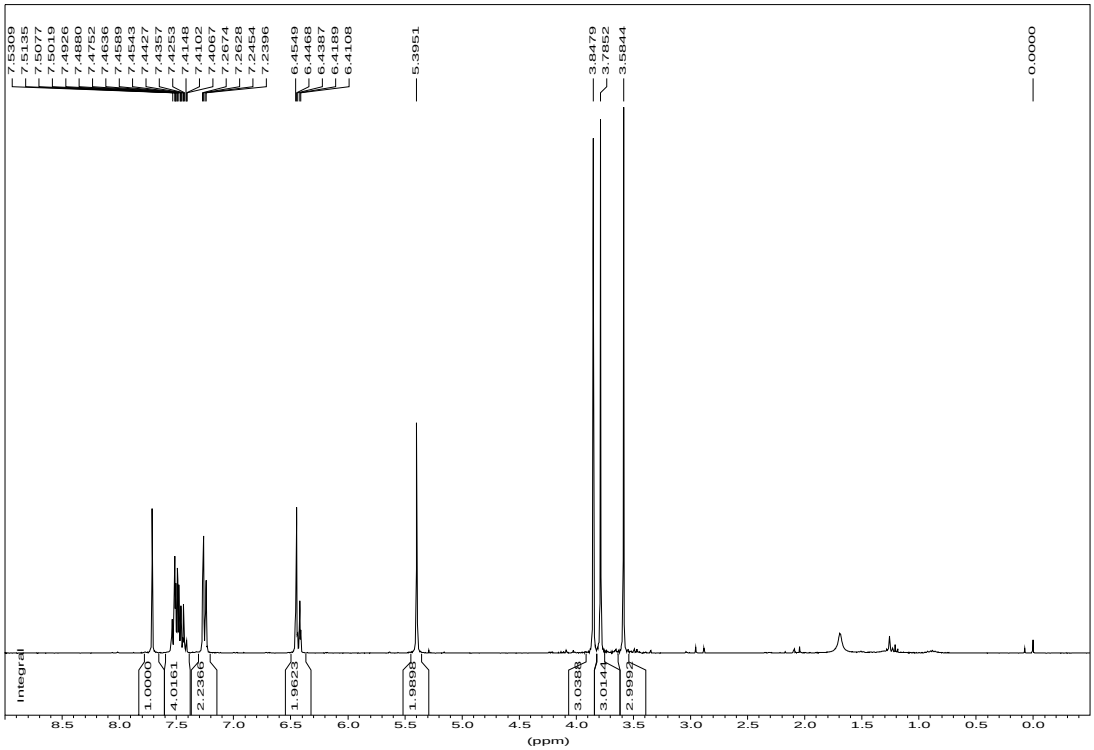
^{1}H NMR of **2-1-12**



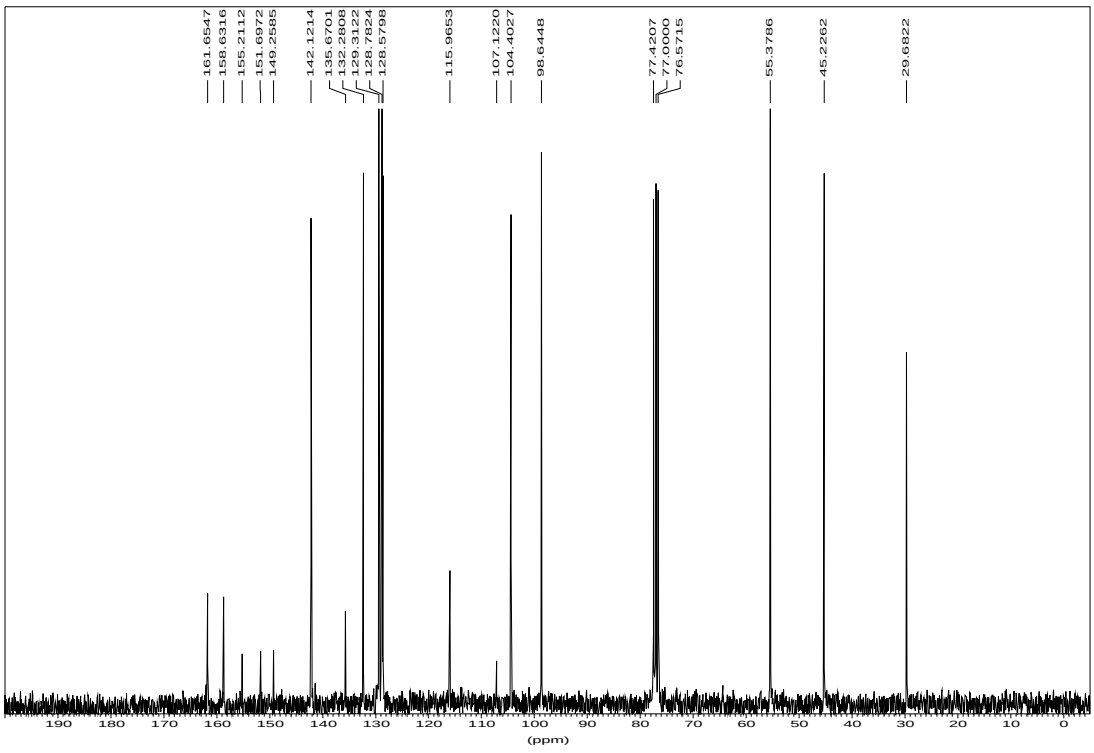
^{13}C NMR of **2-1-12**



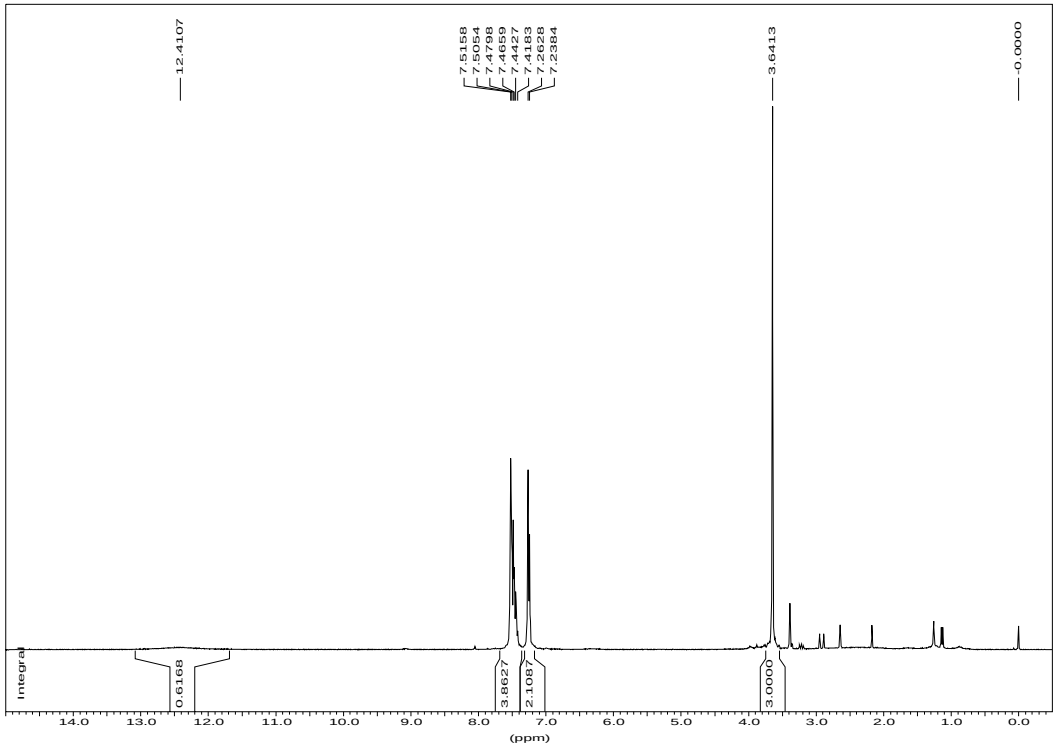
^{1}H NMR of **2-1-13**



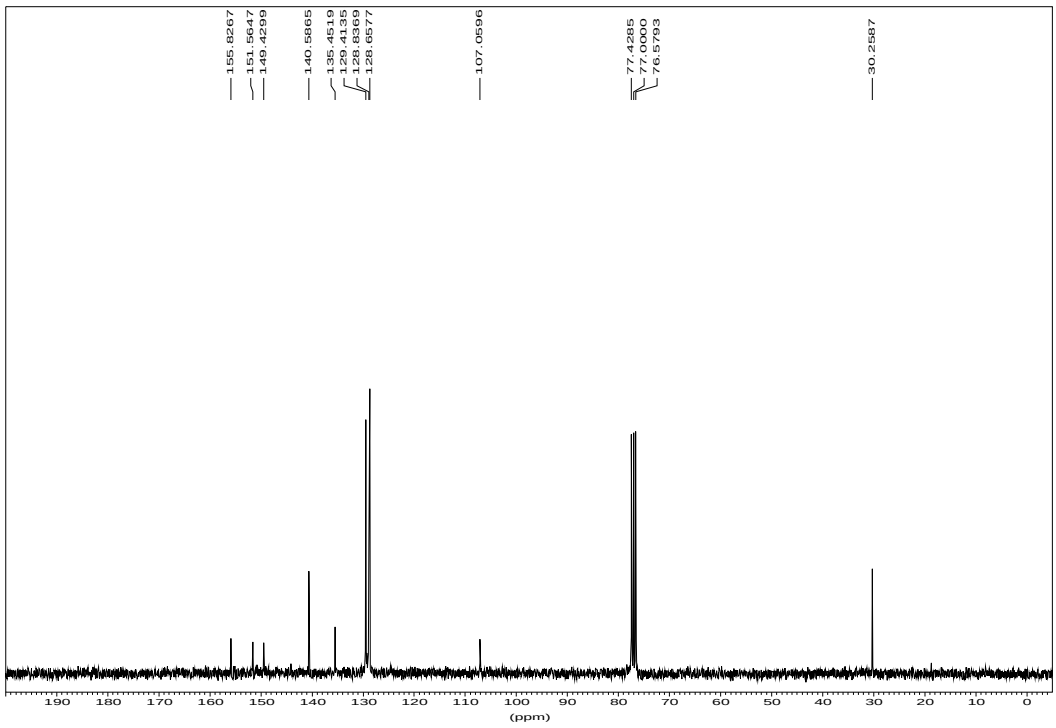
^{13}C NMR of **2-1-13**



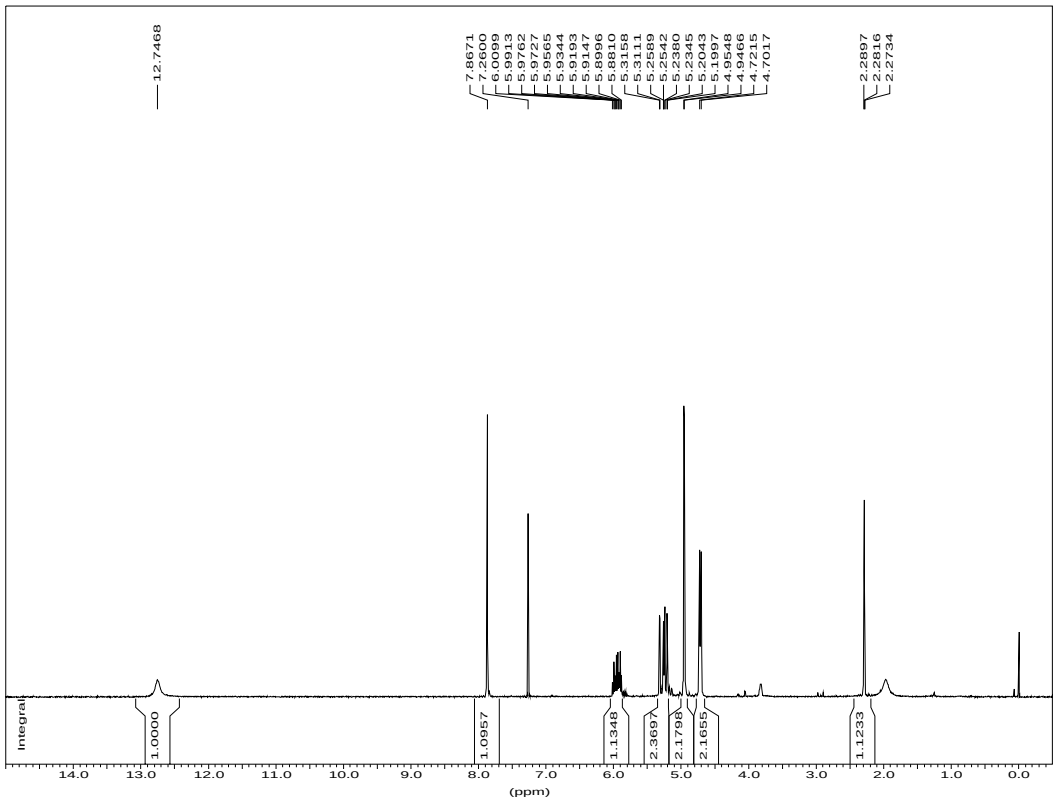
^{1}H NMR of **2-1-7b**



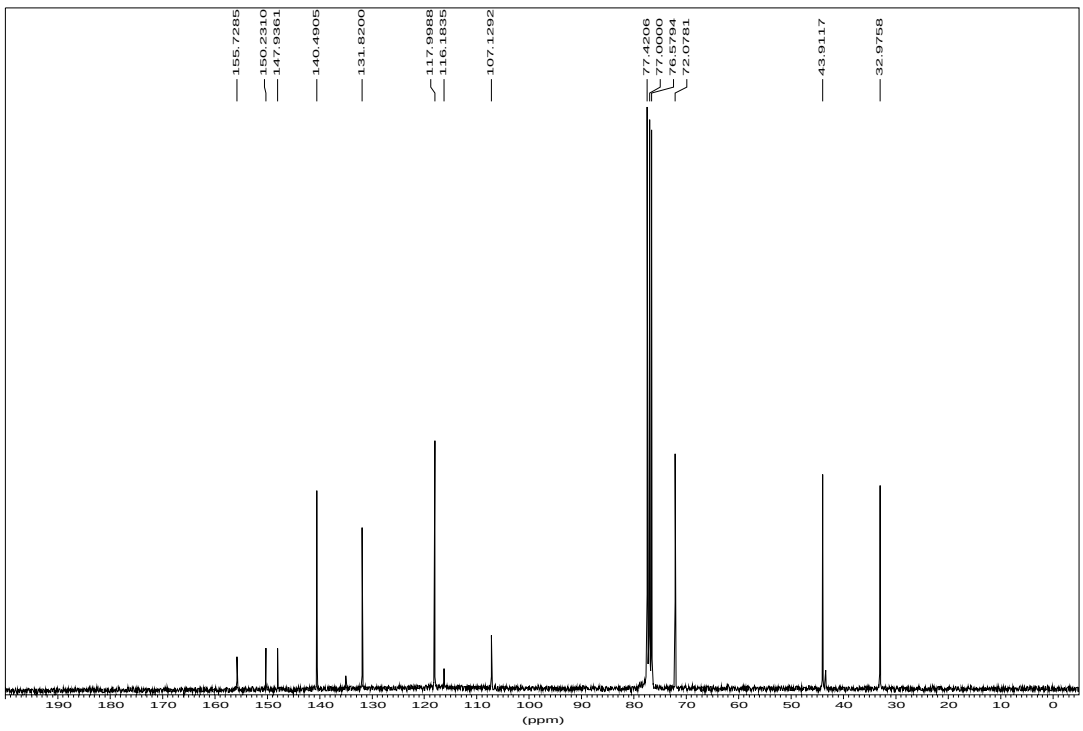
^{13}C NMR of **2-1-7b**



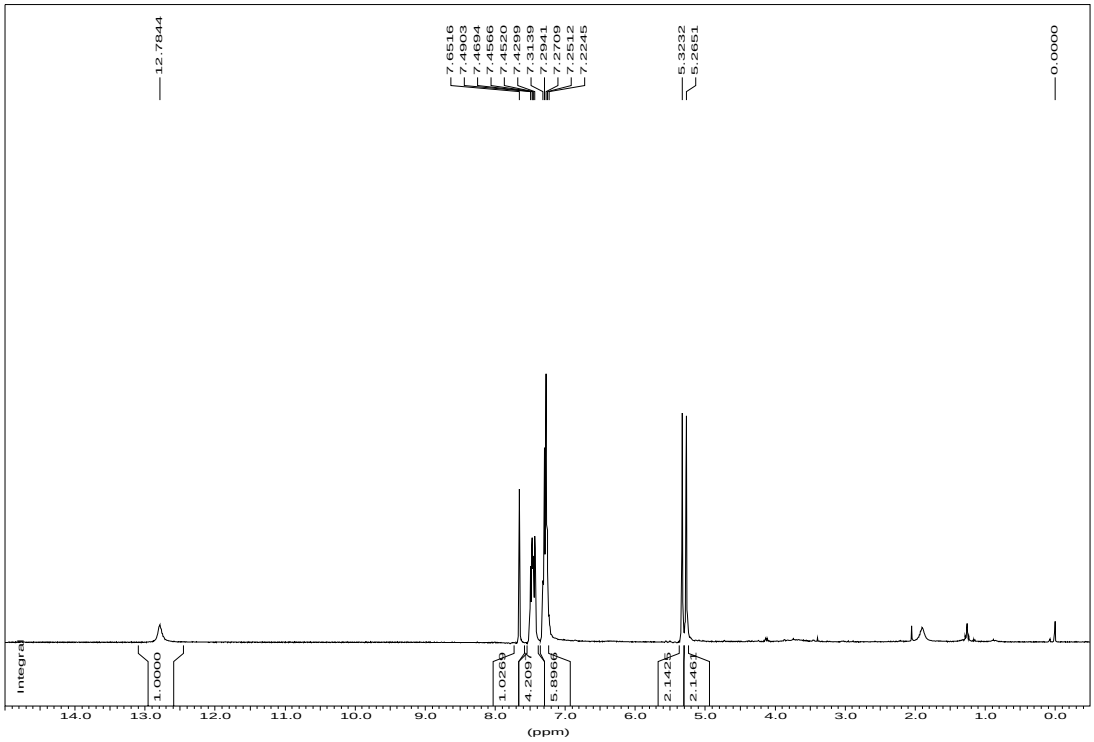
^{1}H NMR of **2-1-7h**



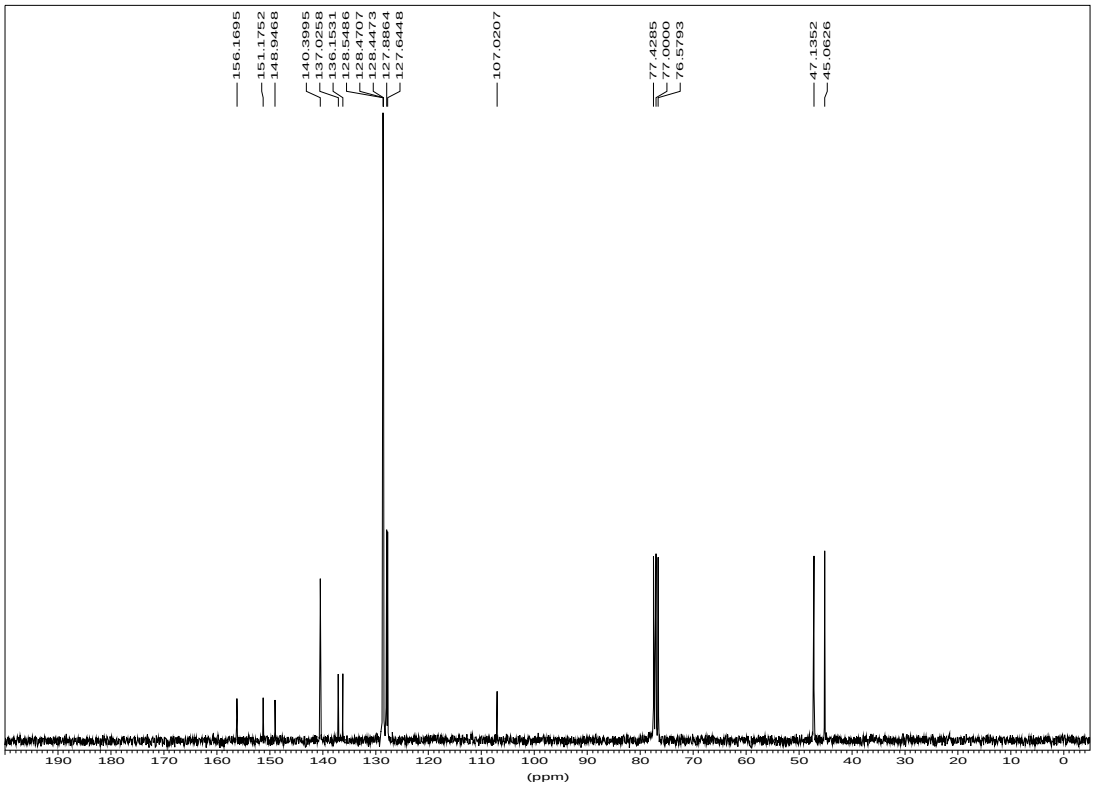
^{13}C NMR of **2-1-7h**



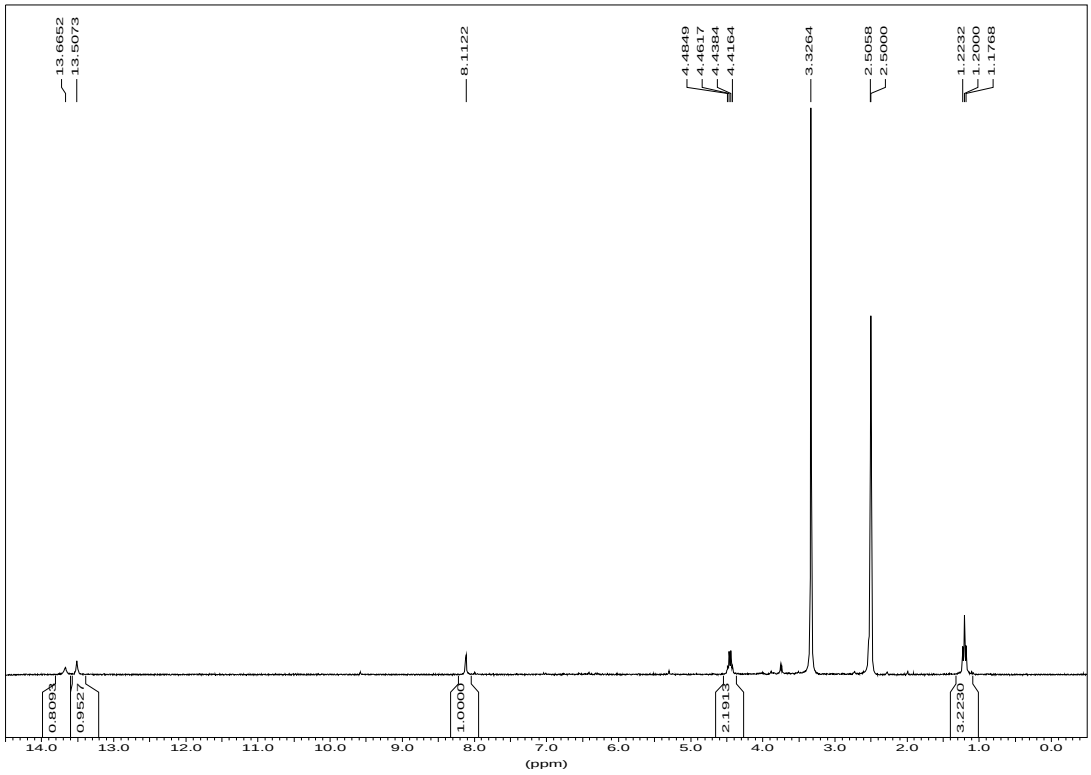
^{1}H NMR of **2-1-7k**



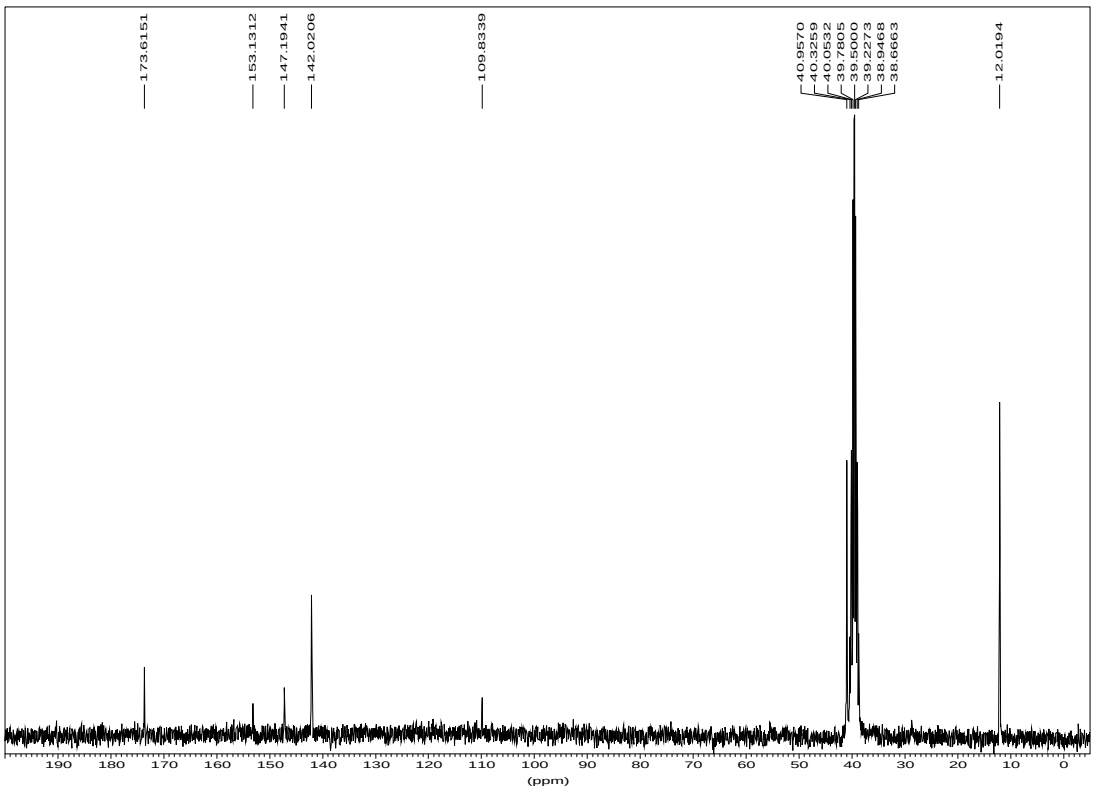
^{13}C NMR of **2-1-7k**



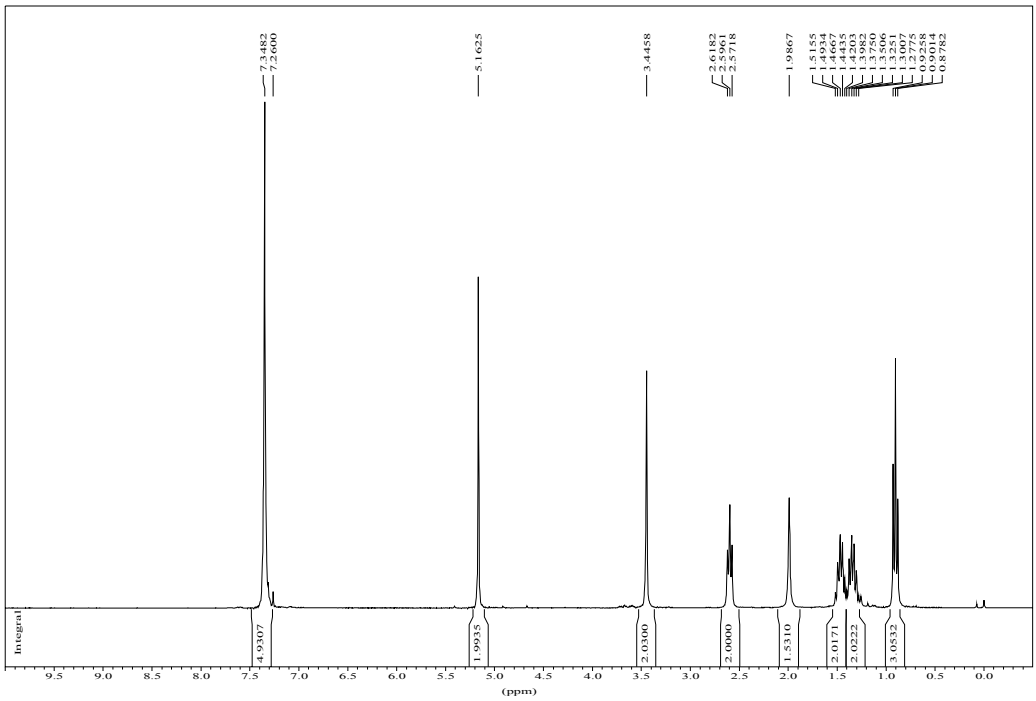
^{1}H NMR of **2-1-7n**



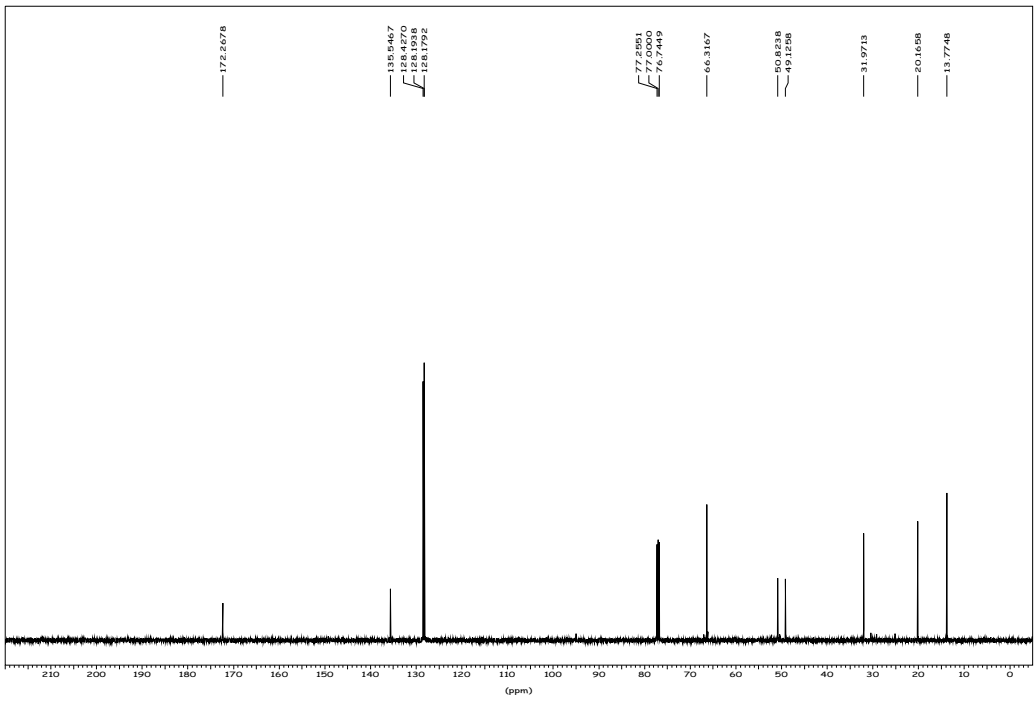
^{13}C NMR of **2-1-7n**



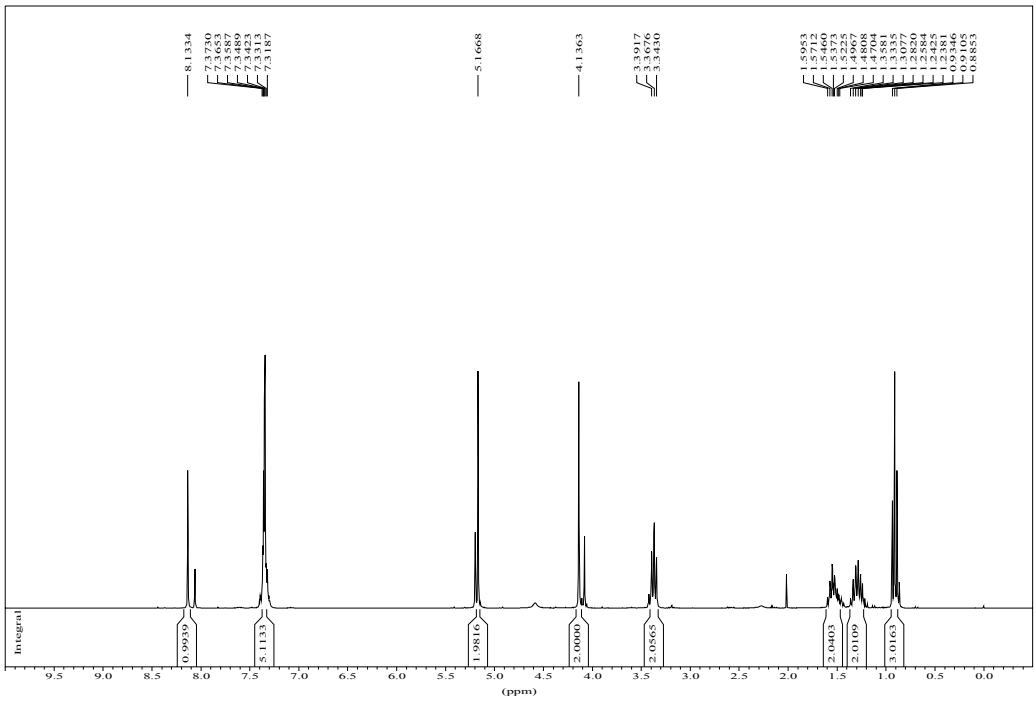
^{1}H NMR of **2-2-10**



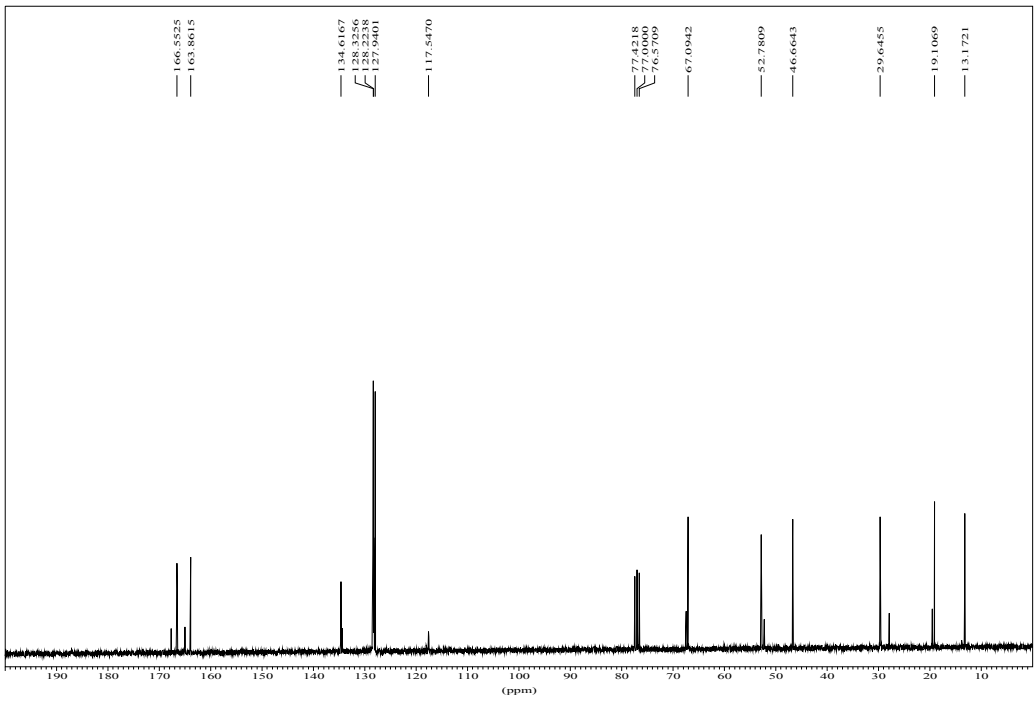
^{13}C NMR of **2-2-10**



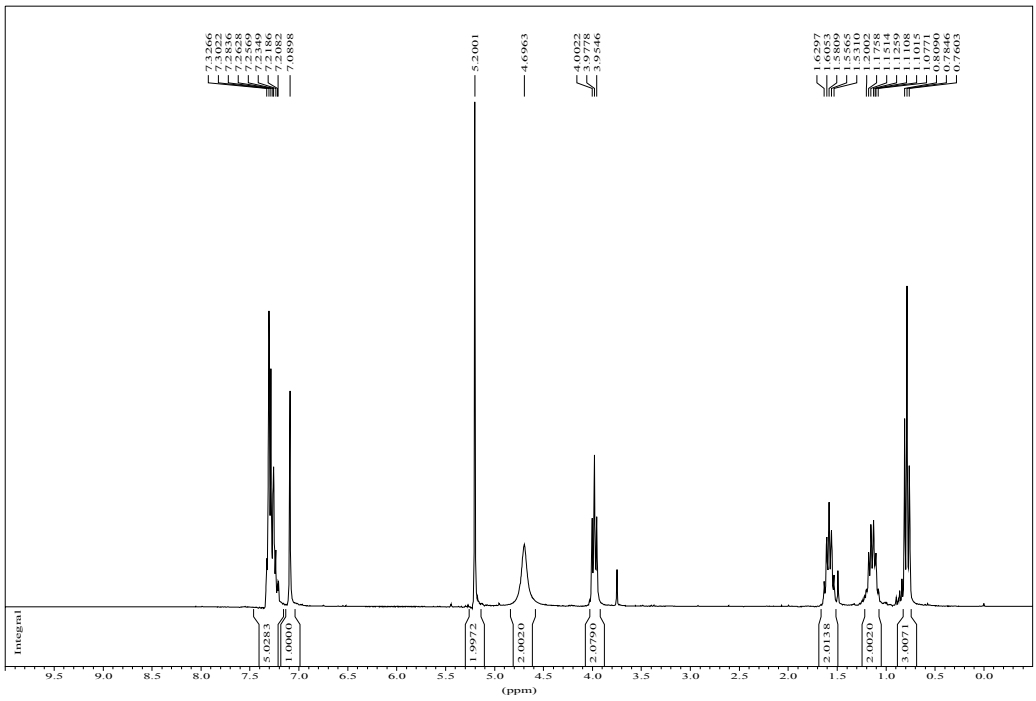
^{1}H NMR of **2-2-11**



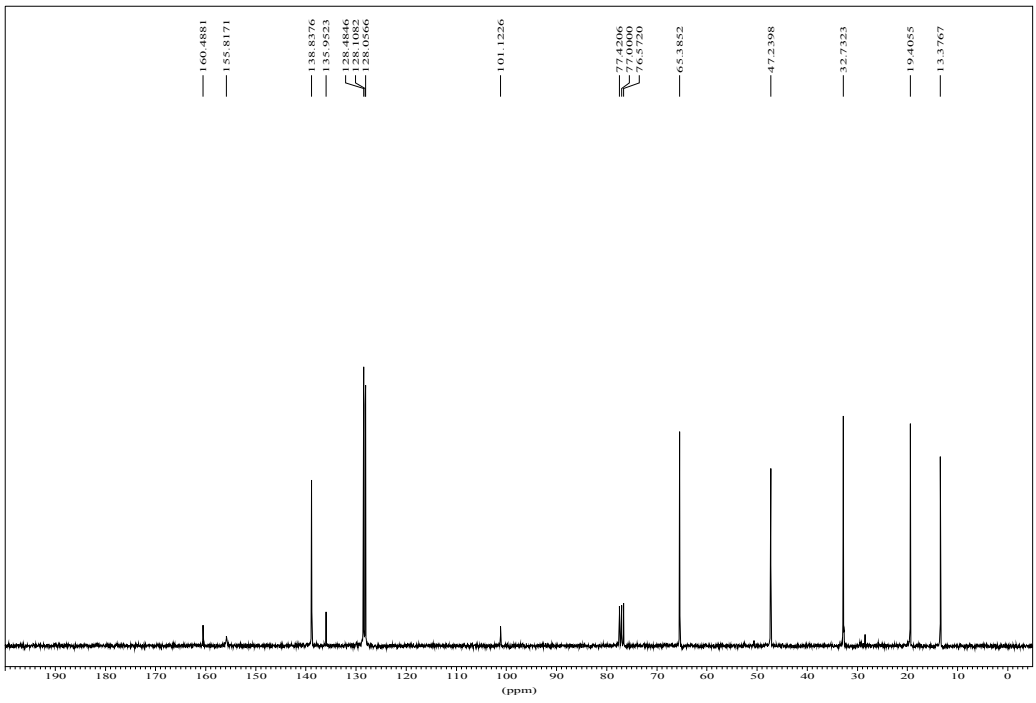
^{13}C NMR of **2-2-11**



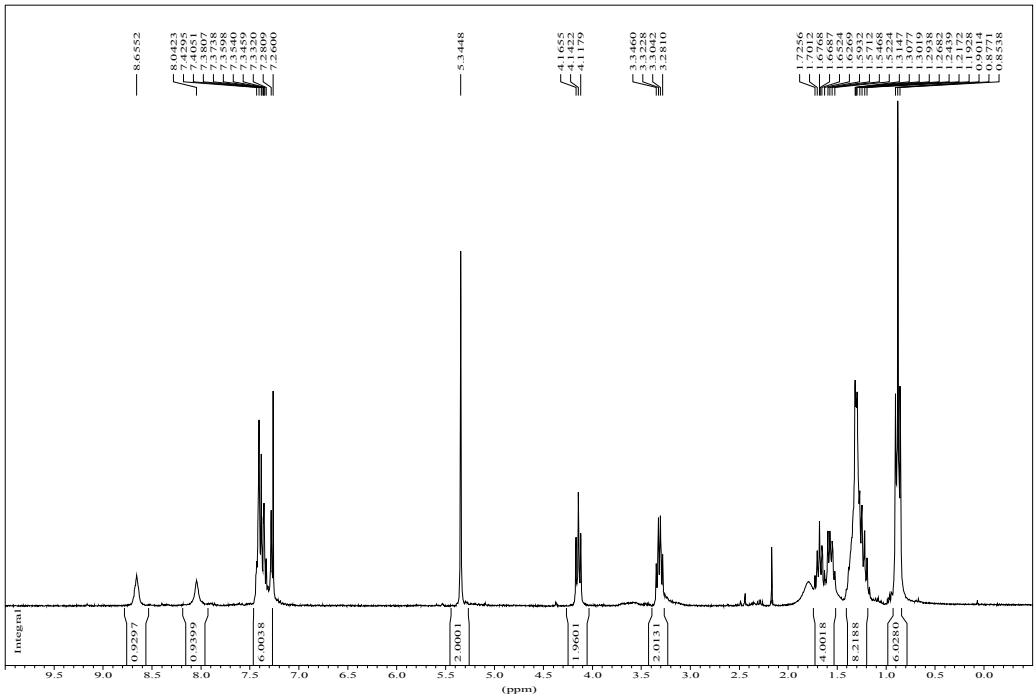
^{1}H NMR of **2-2-12**



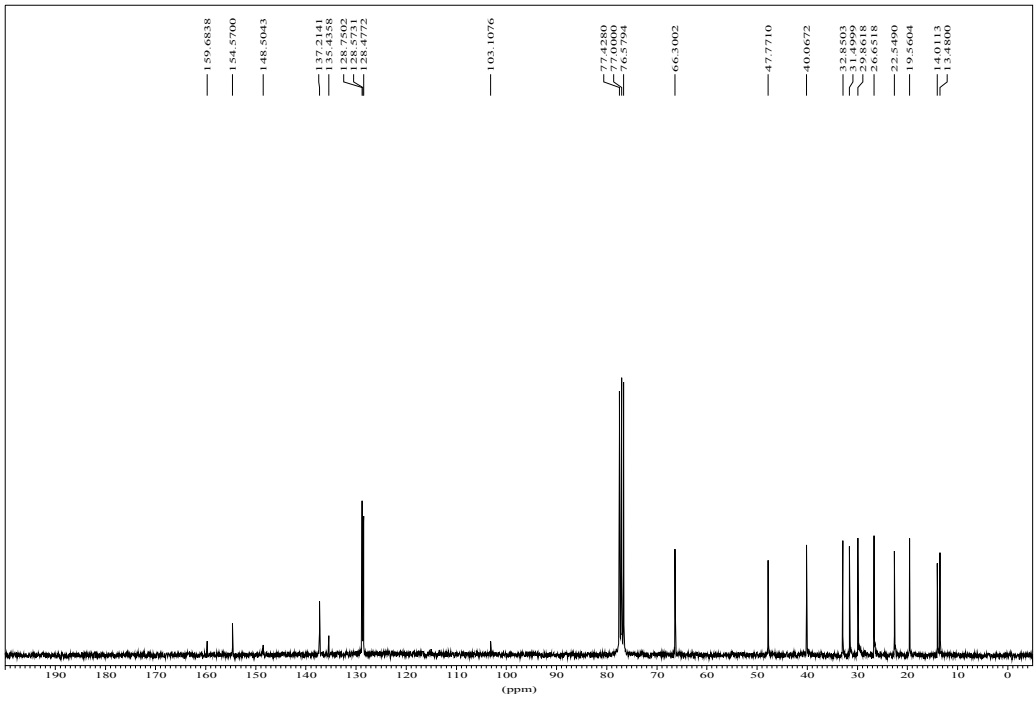
^{13}C NMR of **2-2-12**



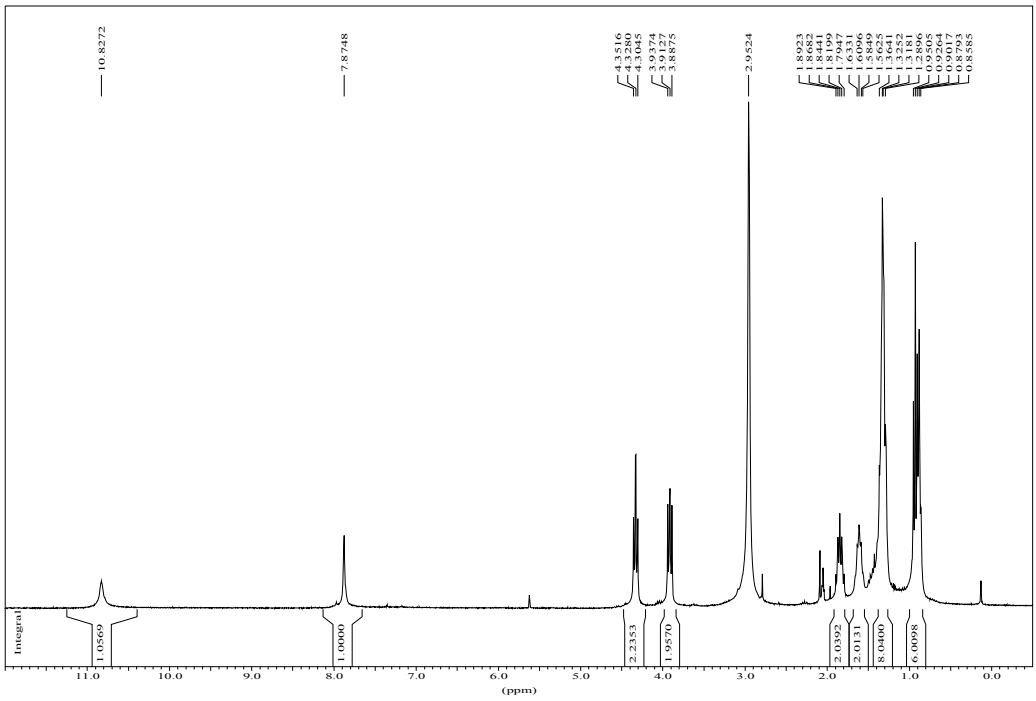
^{1}H NMR of **2-2-13**



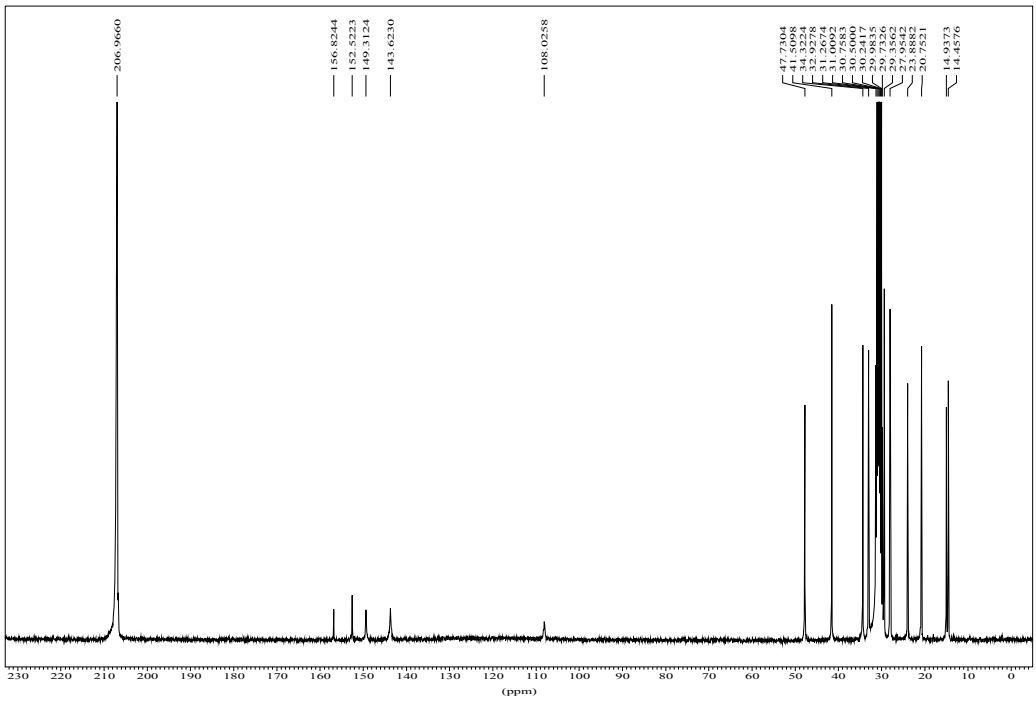
^{13}C NMR of **2-2-13**



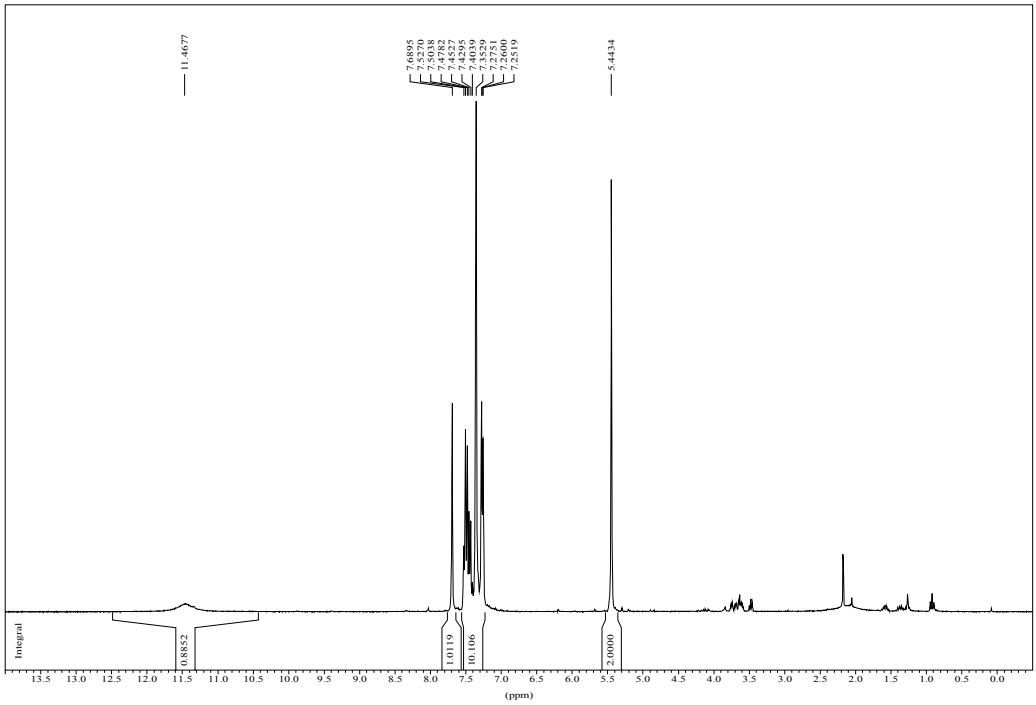
^{1}H NMR of **2-2-7a**



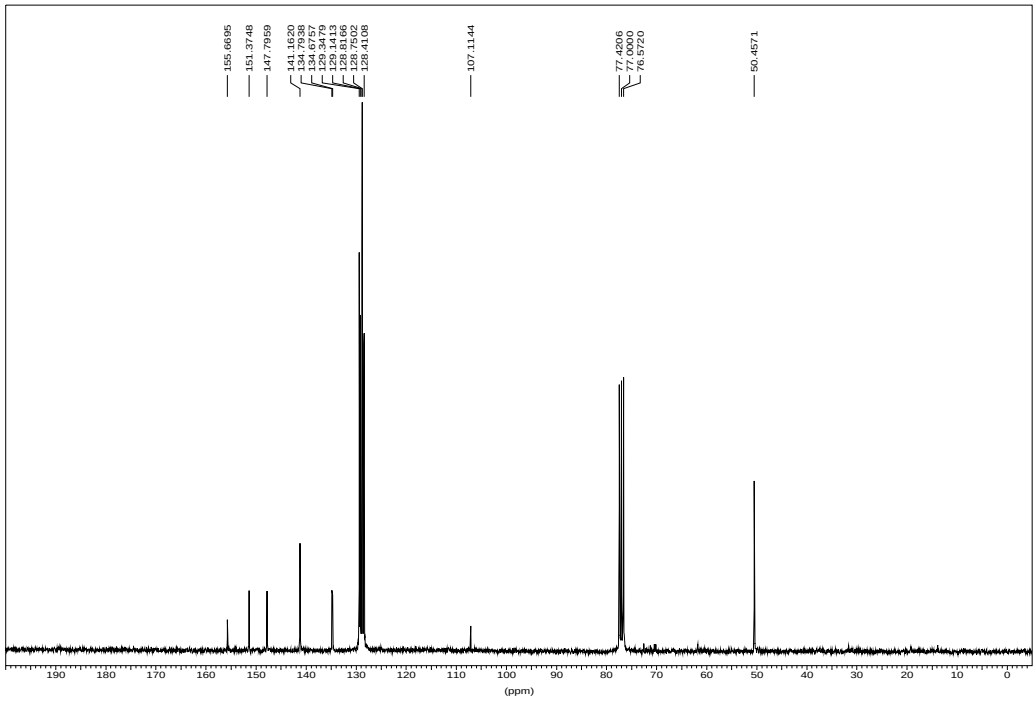
^{13}C NMR of **2-2-7a**



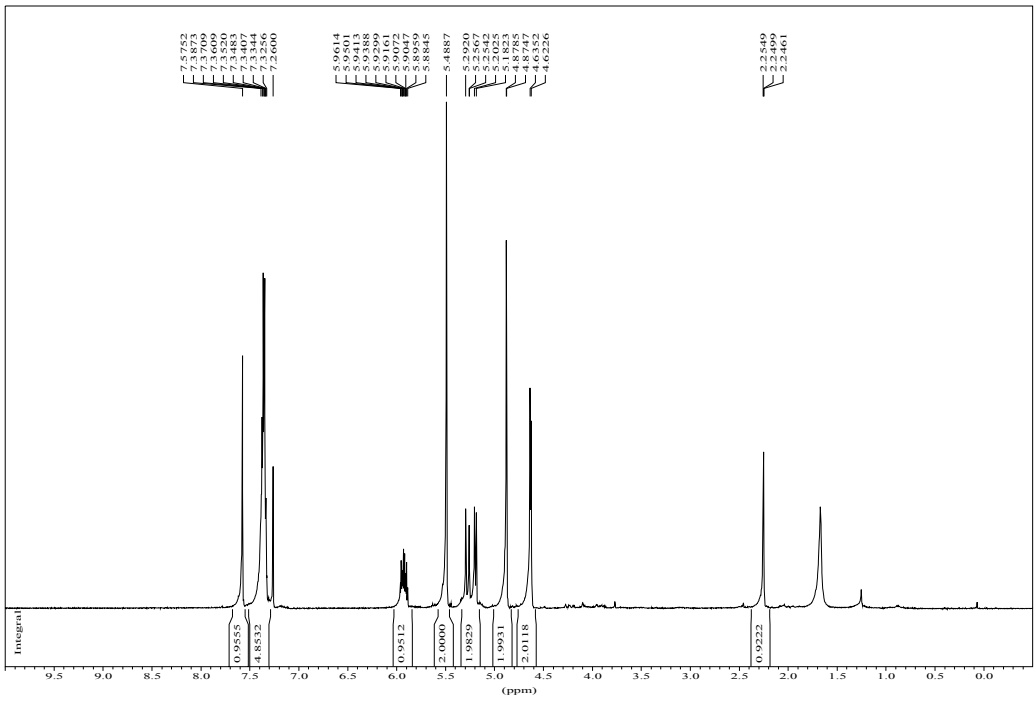
^{1}H NMR of **2-2-7f**



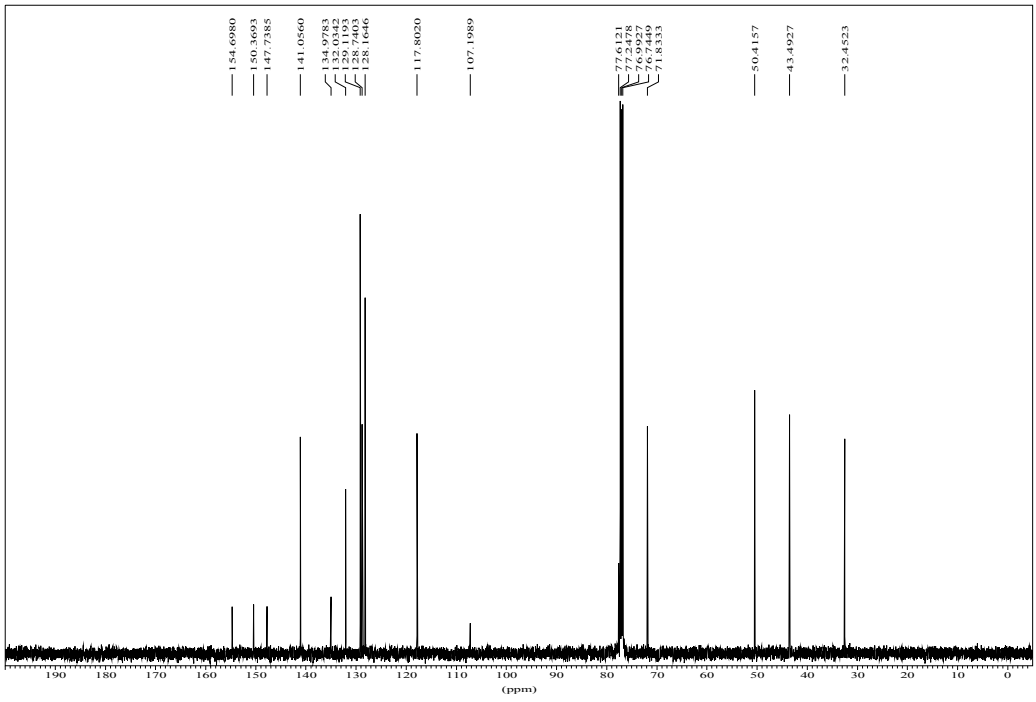
^{13}C NMR of **2-2-7f**



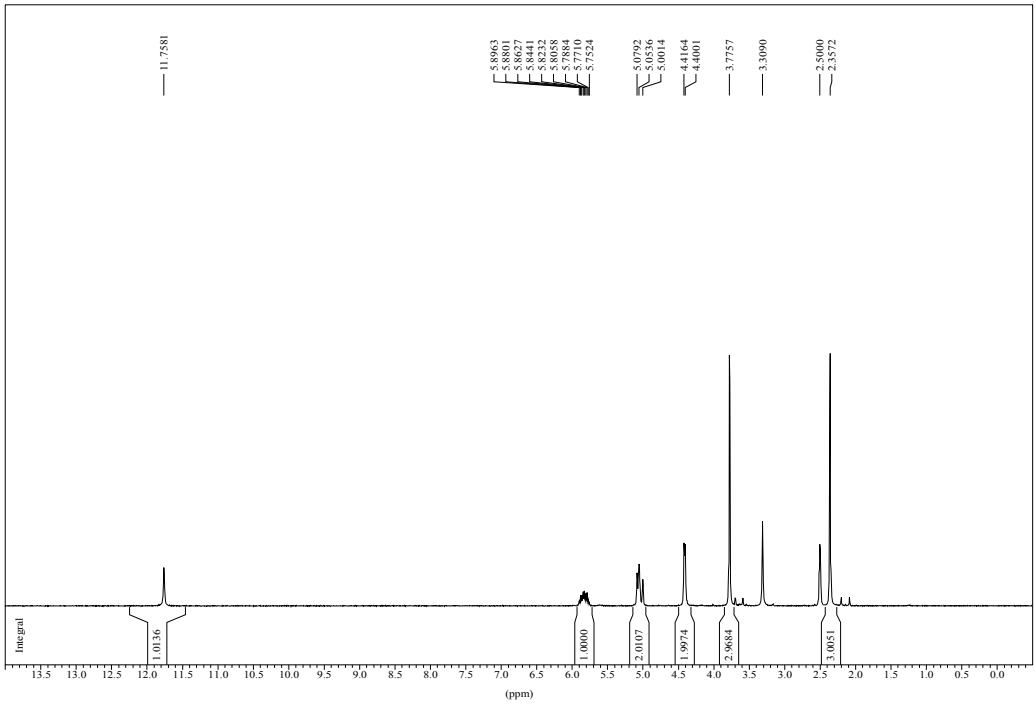
^{1}H NMR of **2-2-7l**



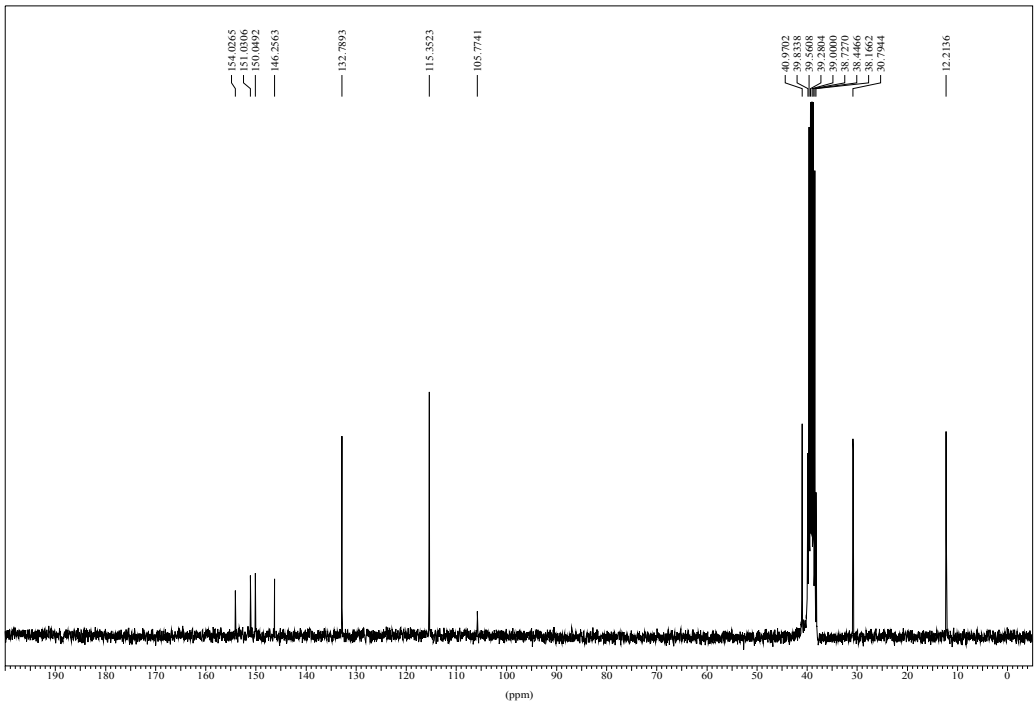
^{13}C NMR of **2-2-7l**



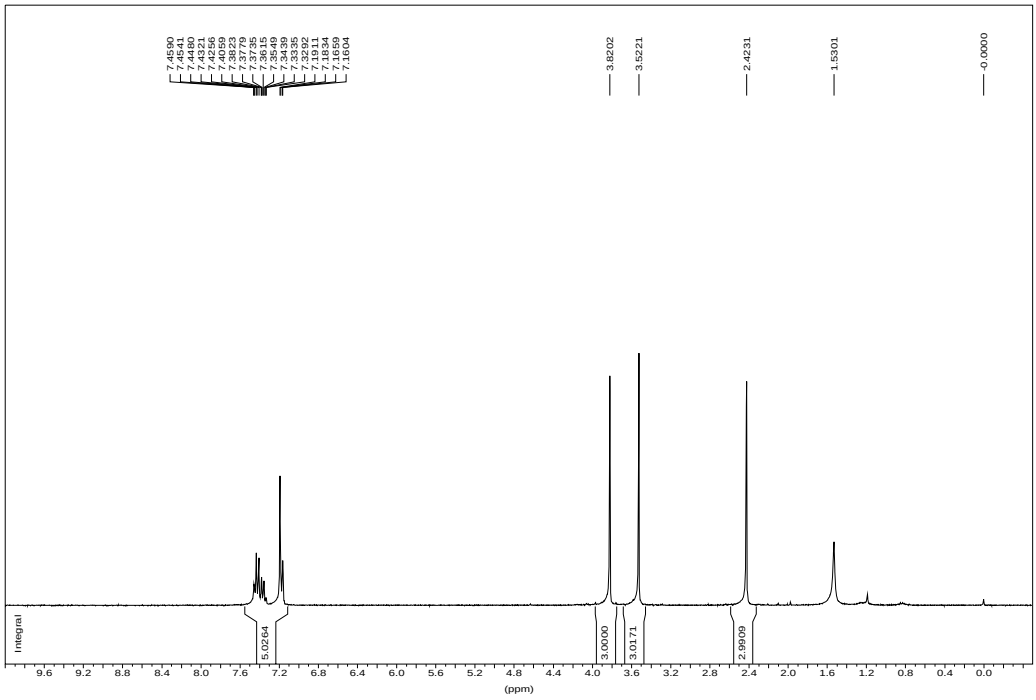
^{1}H NMR of **2-2-7q**



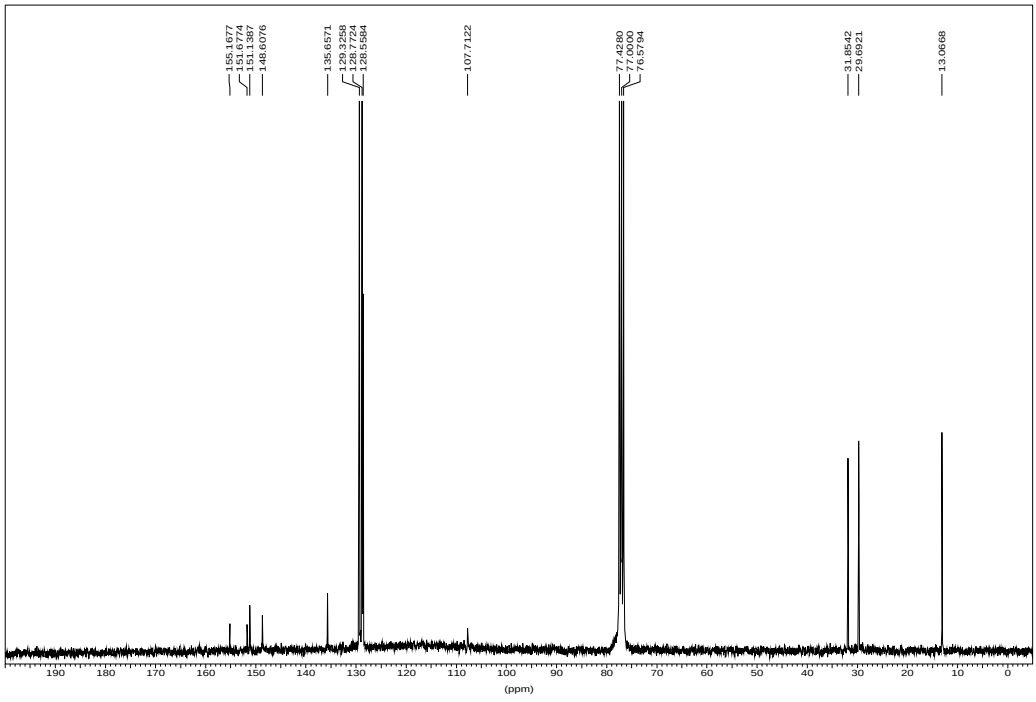
^{13}C NMR of **2-2-7q**



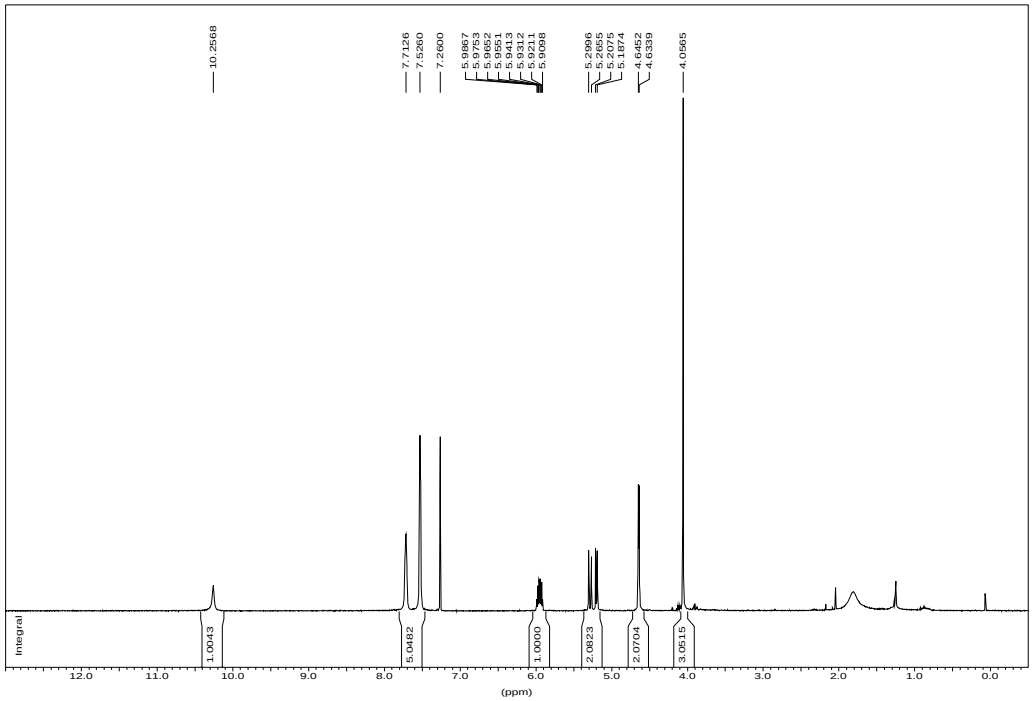
^{1}H NMR of **2-2-7t**



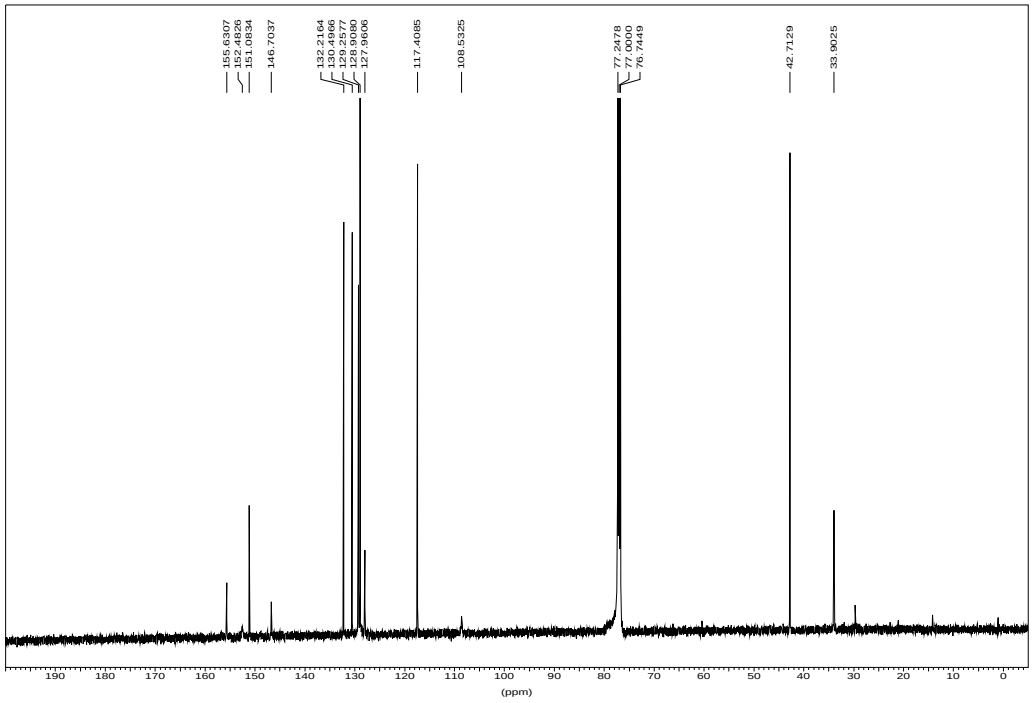
^{13}C NMR of **2-2-7t**



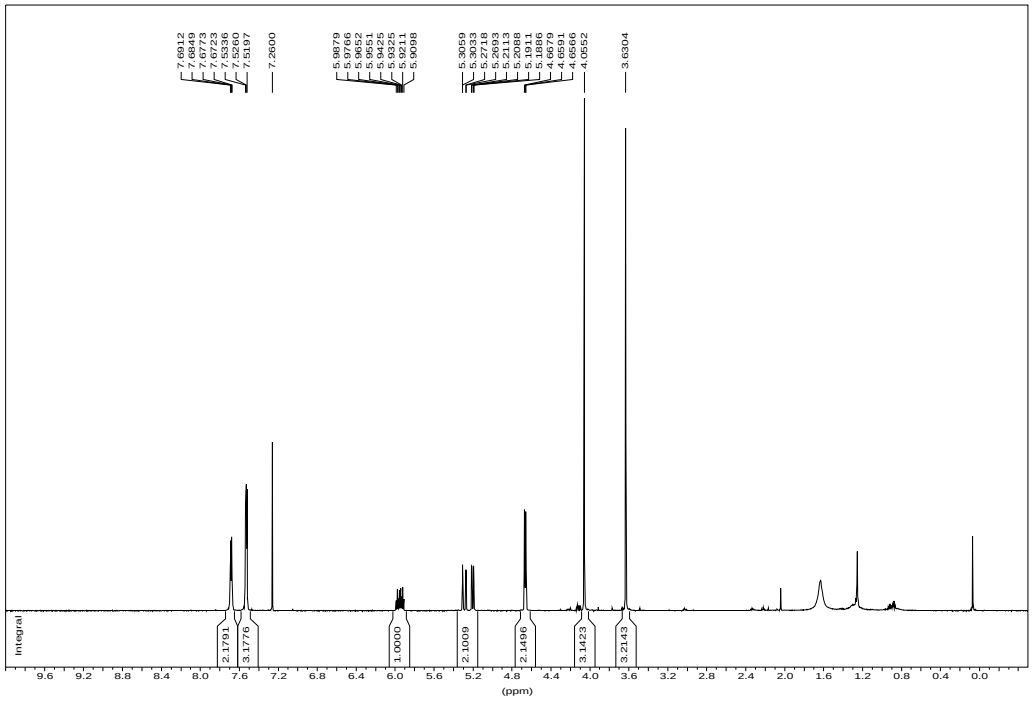
^{1}H NMR of **2-2-7u**



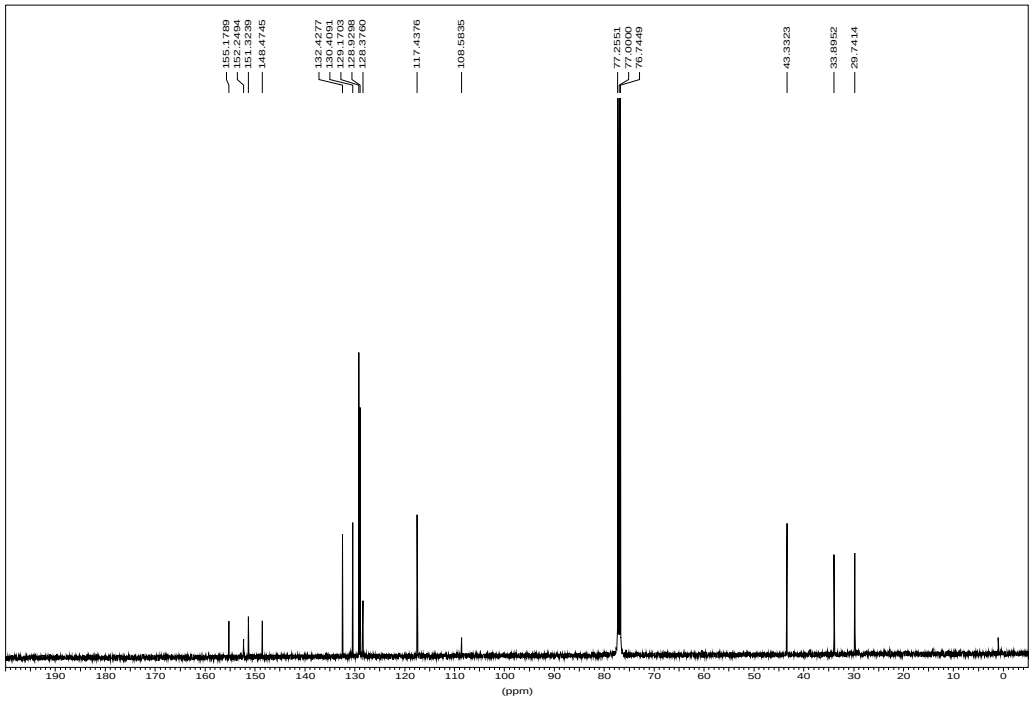
^{13}C NMR of **2-2-7u**



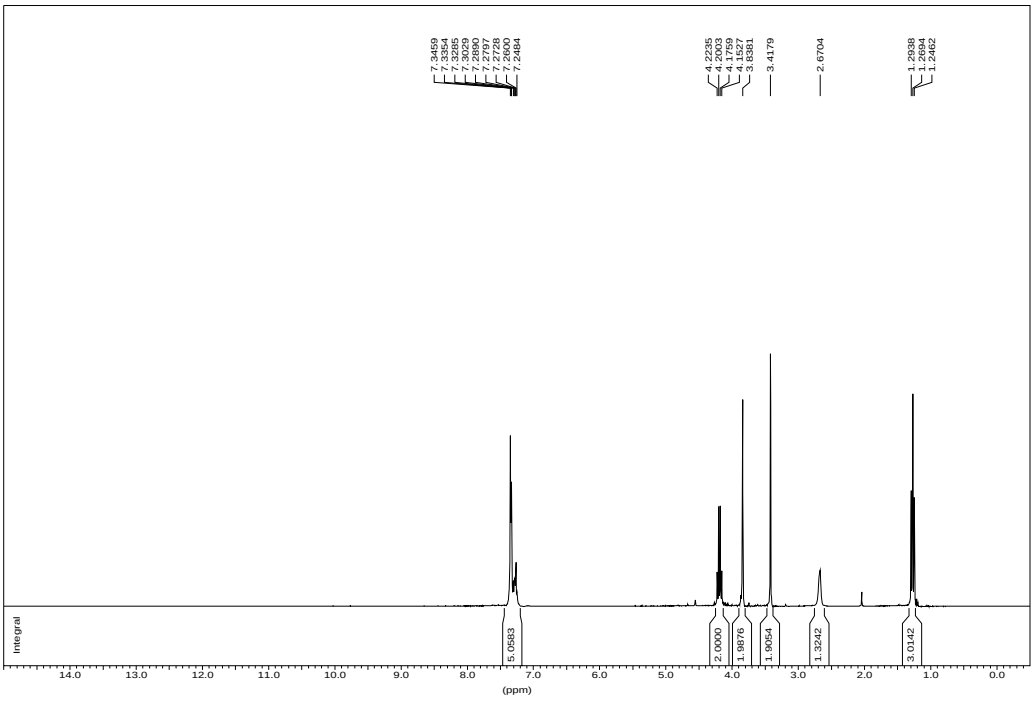
^{1}H NMR of **2-2-7v**



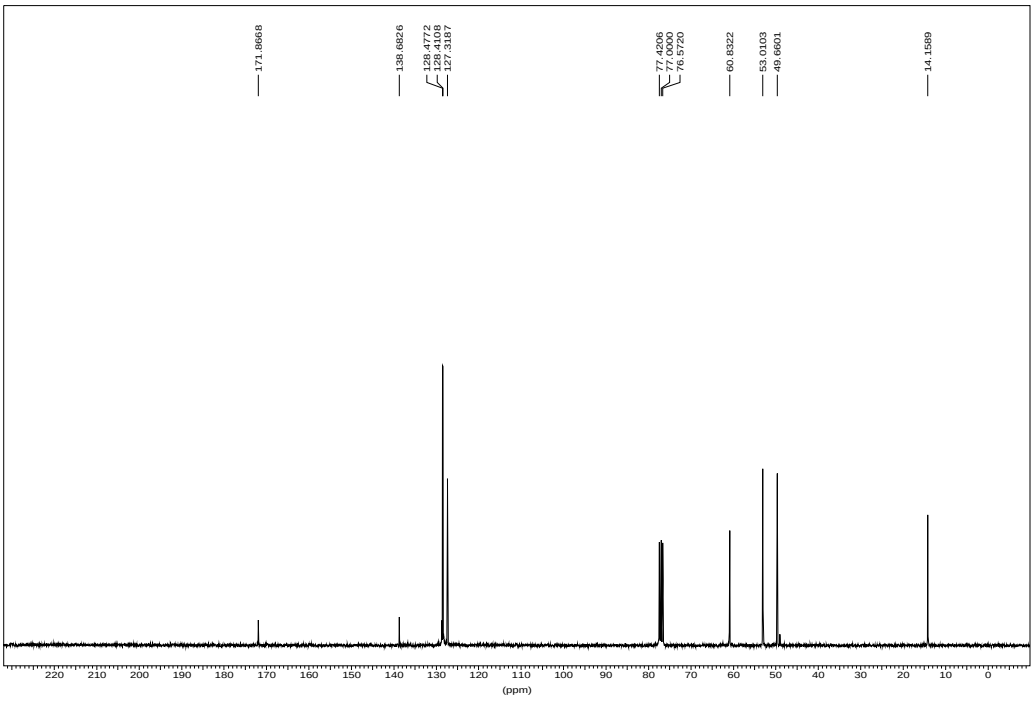
^{13}C NMR of **2-2-7v**



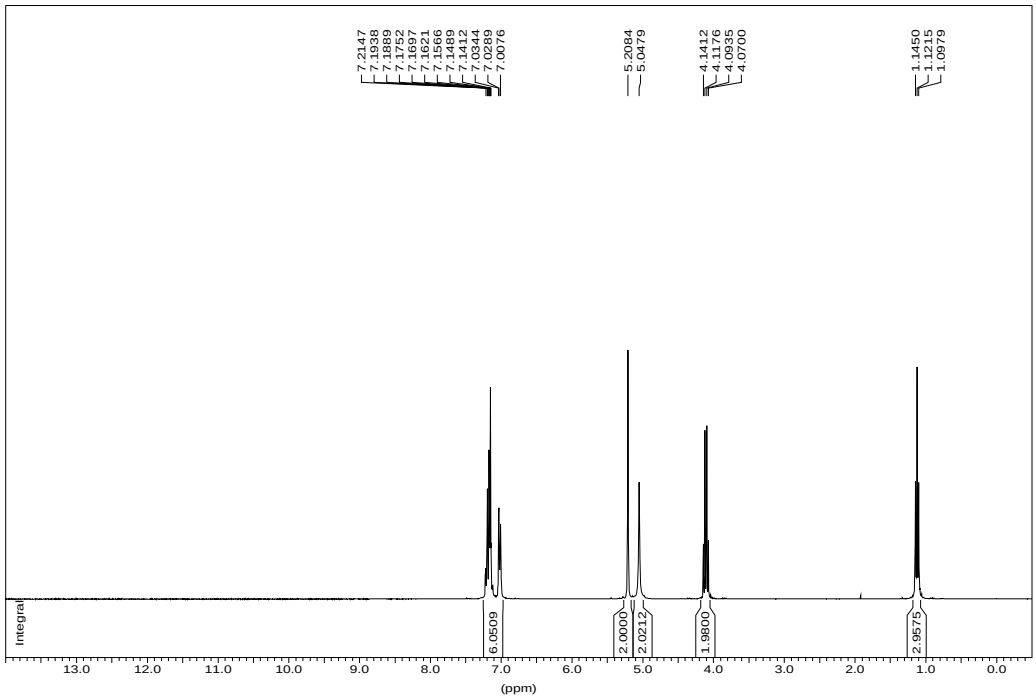
^{1}H NMR of **3-2**



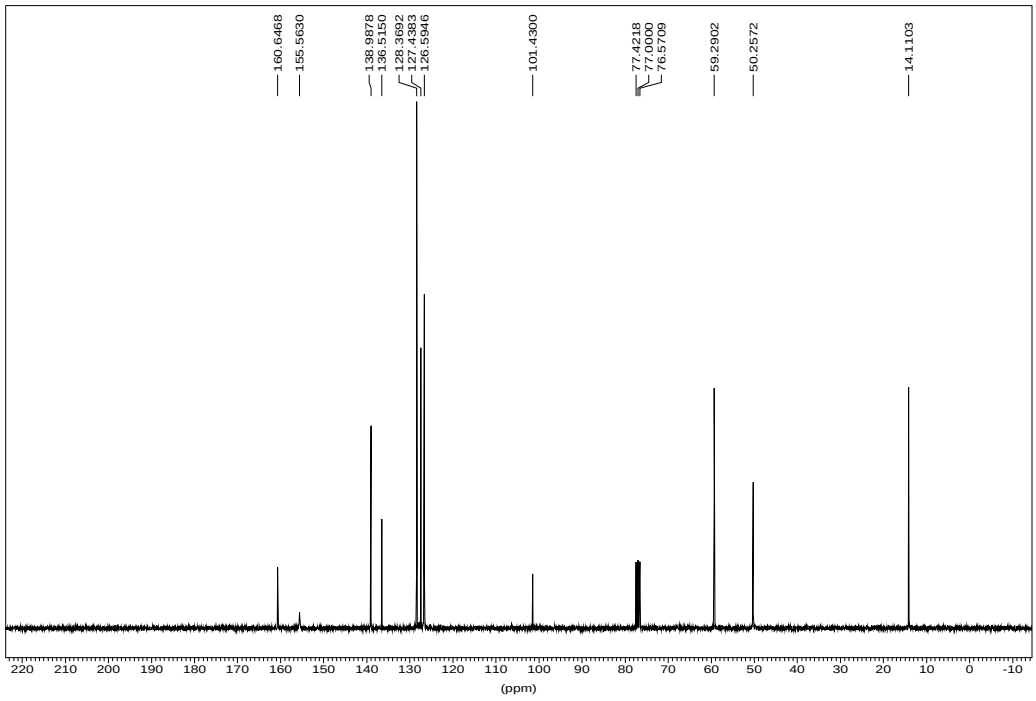
^{13}C NMR of **3-2**



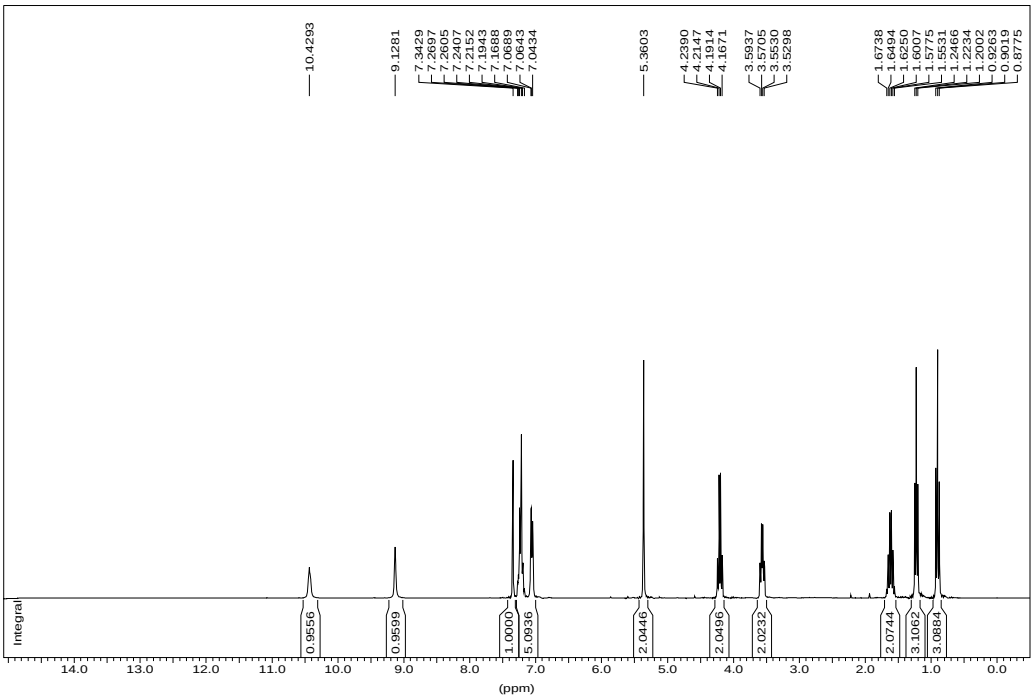
^{1}H NMR of **3-3**



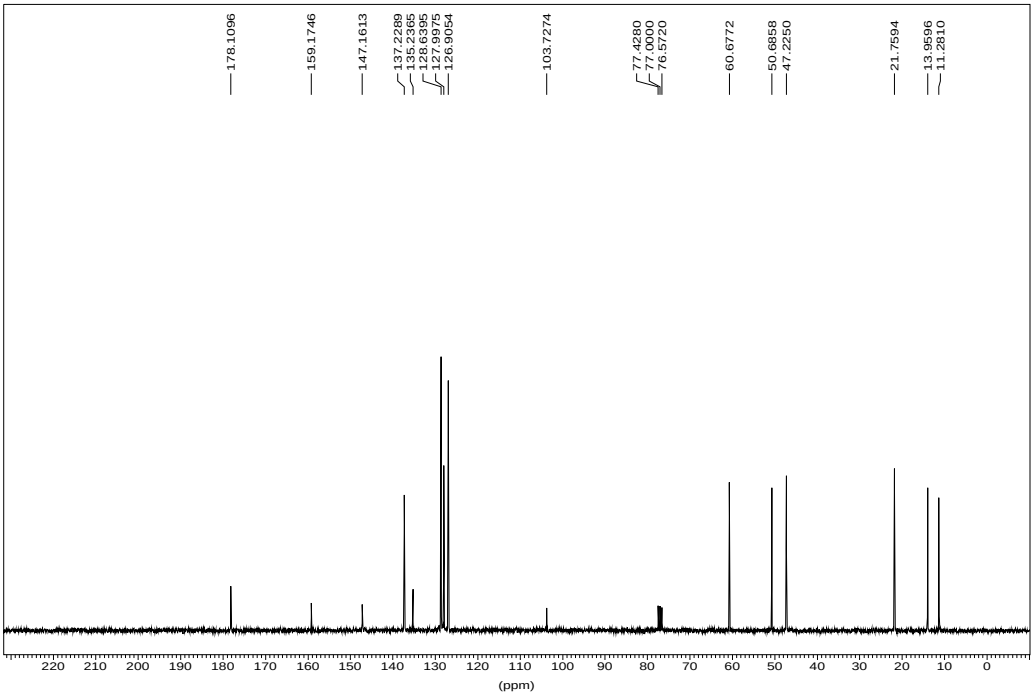
^{13}C NMR of **3-3**



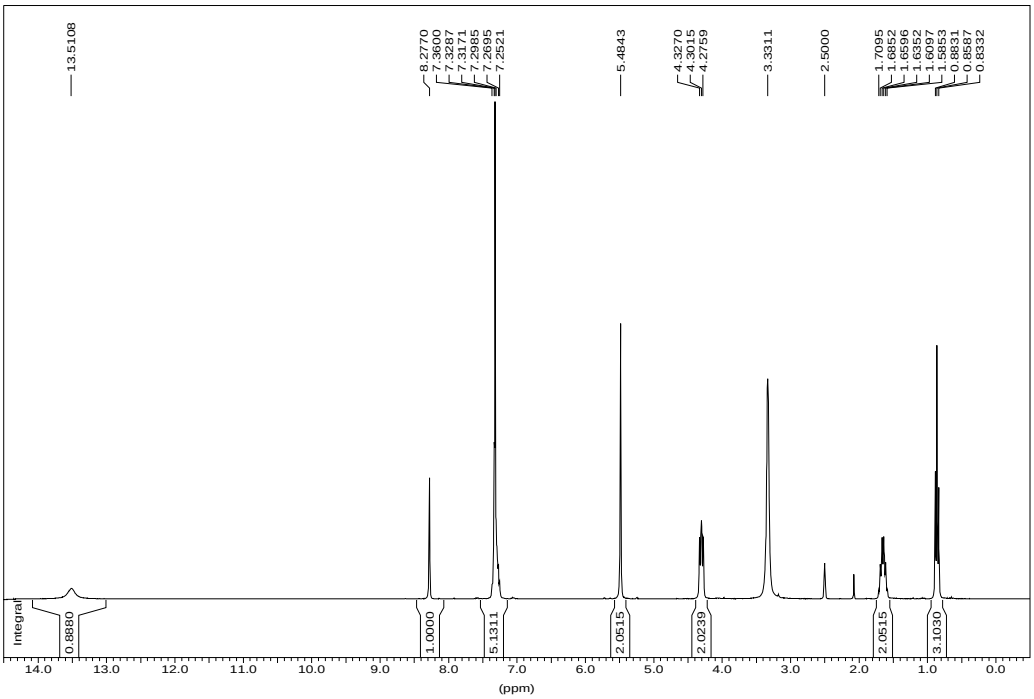
^{1}H NMR of **3-4b**



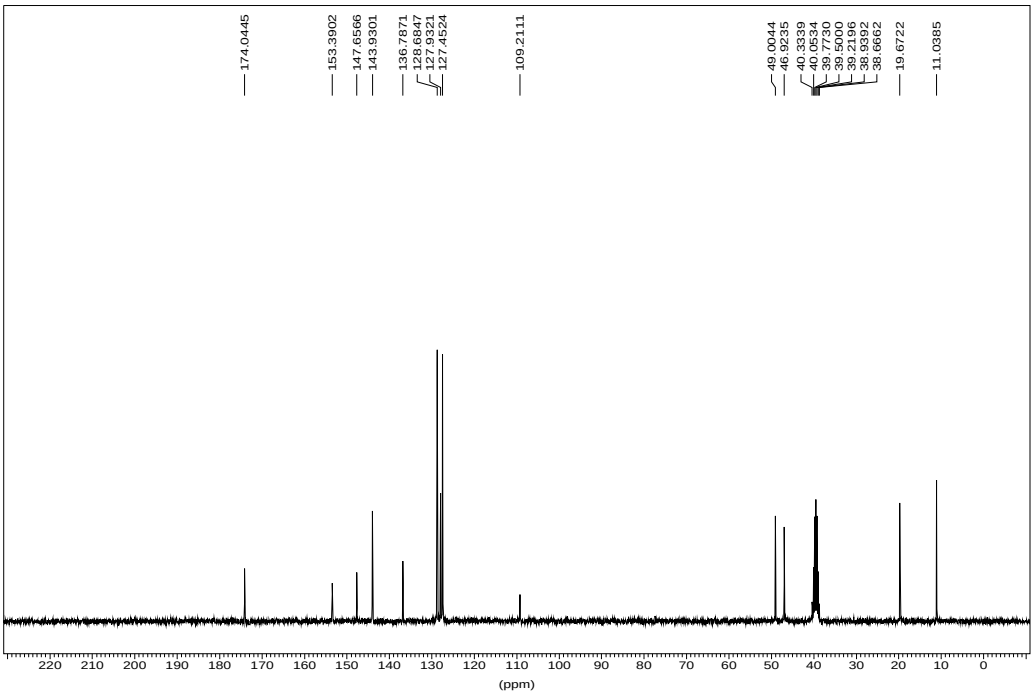
^{13}C NMR of **3-4b**



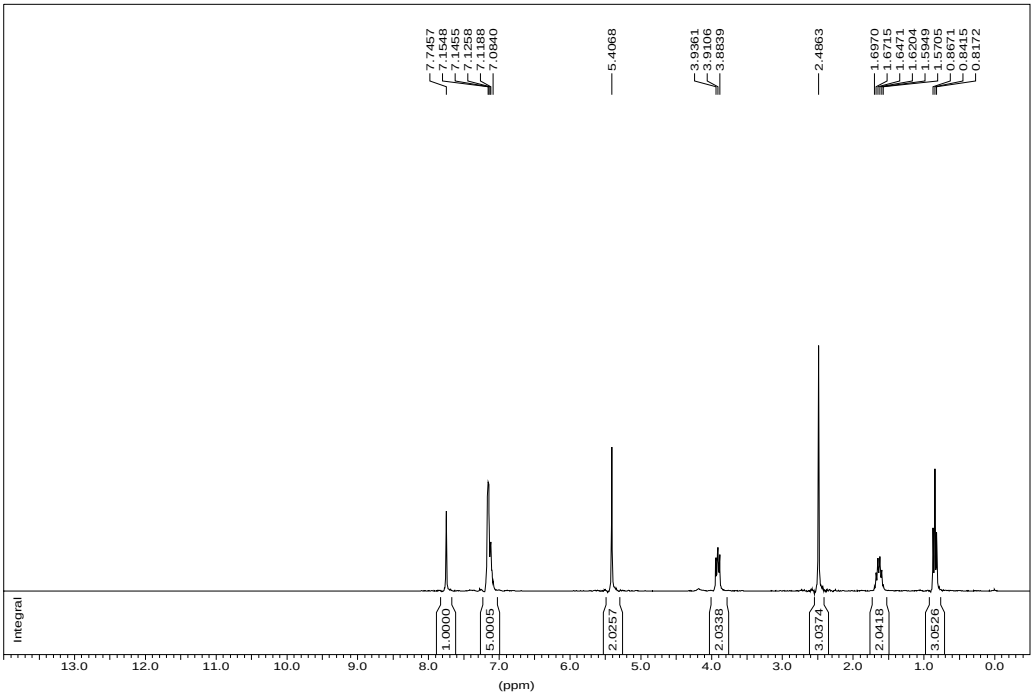
^{1}H NMR of **3-5b**



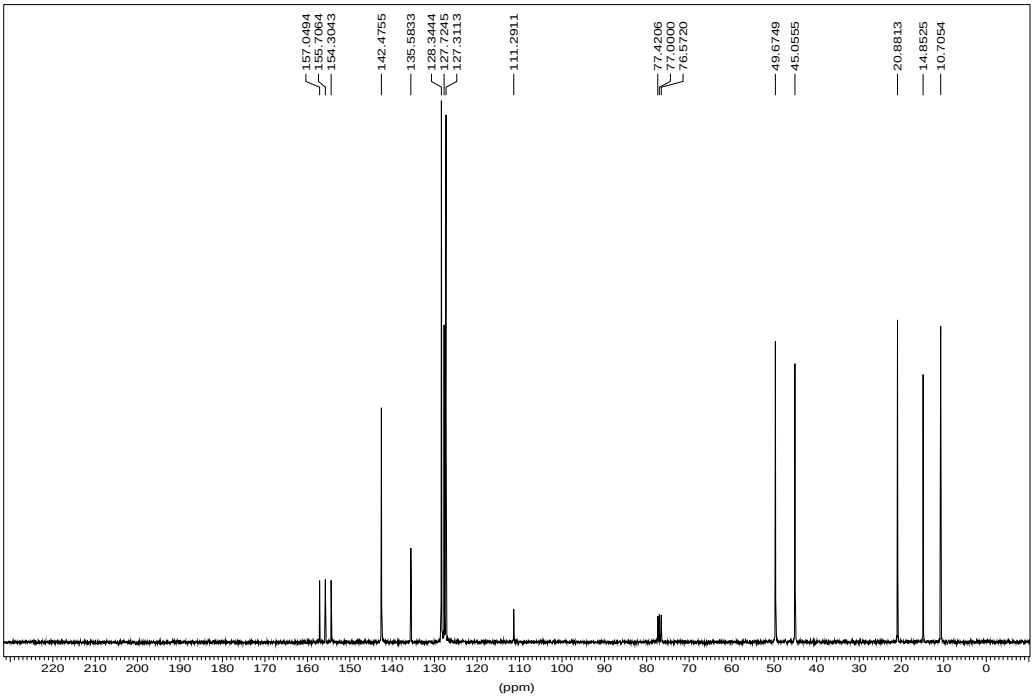
^{13}C NMR of **3-5b**



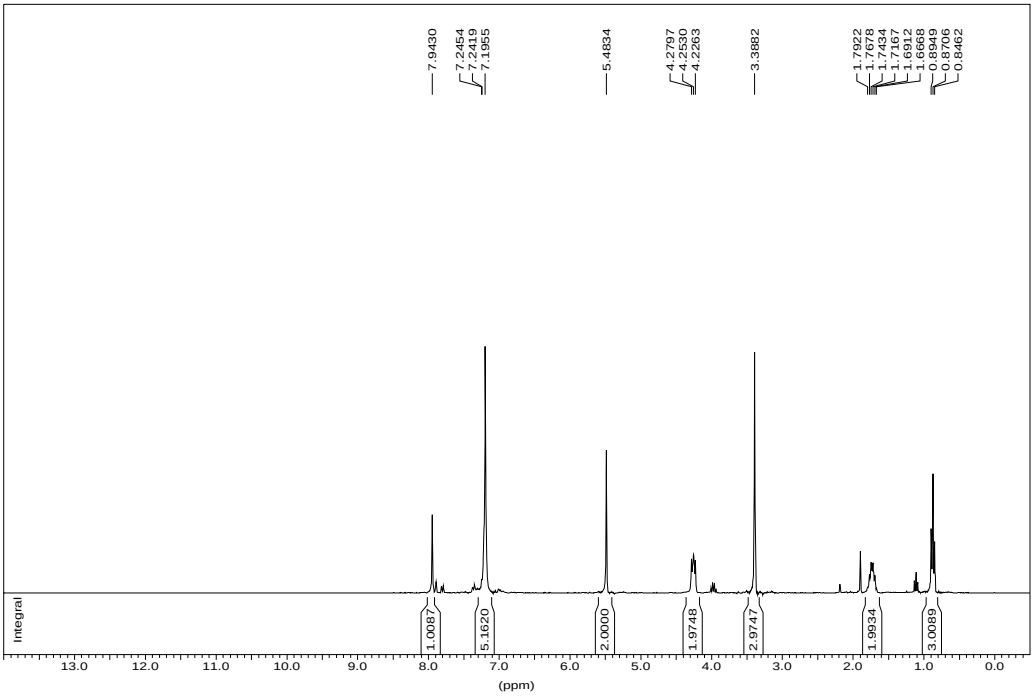
^{1}H NMR of **3-6b**



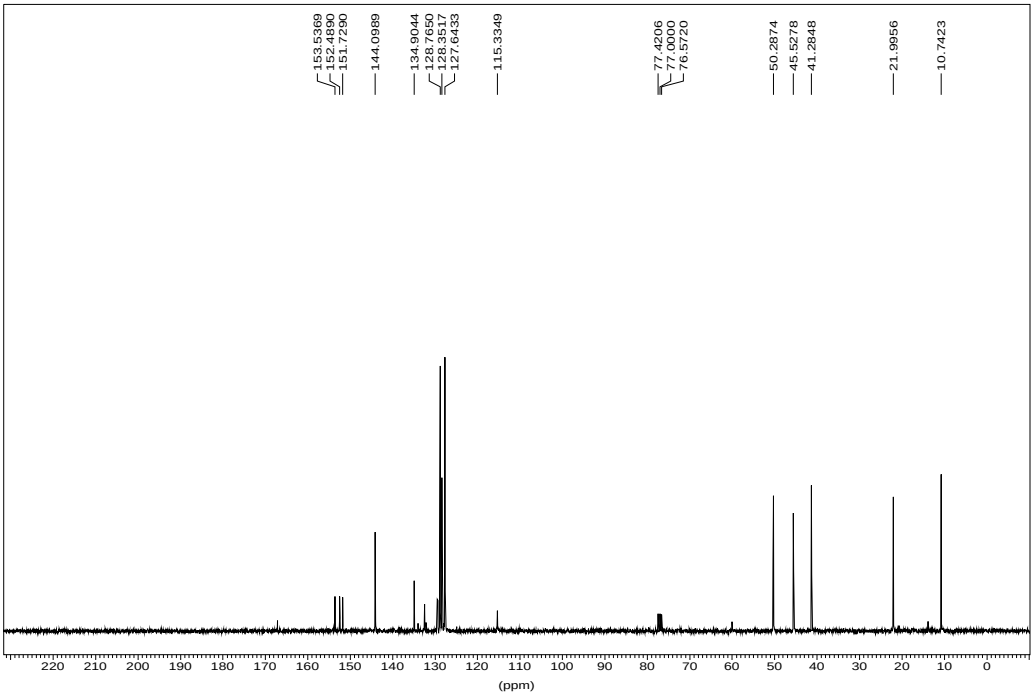
^{13}C NMR of **3-6b**



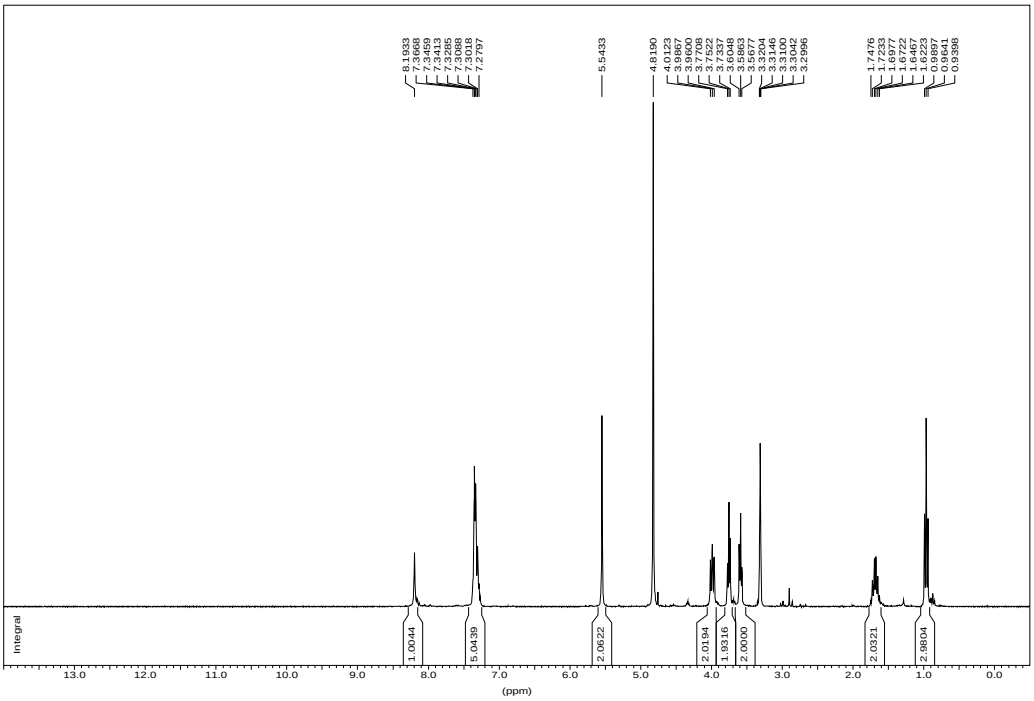
^{1}H NMR of **3-7b**



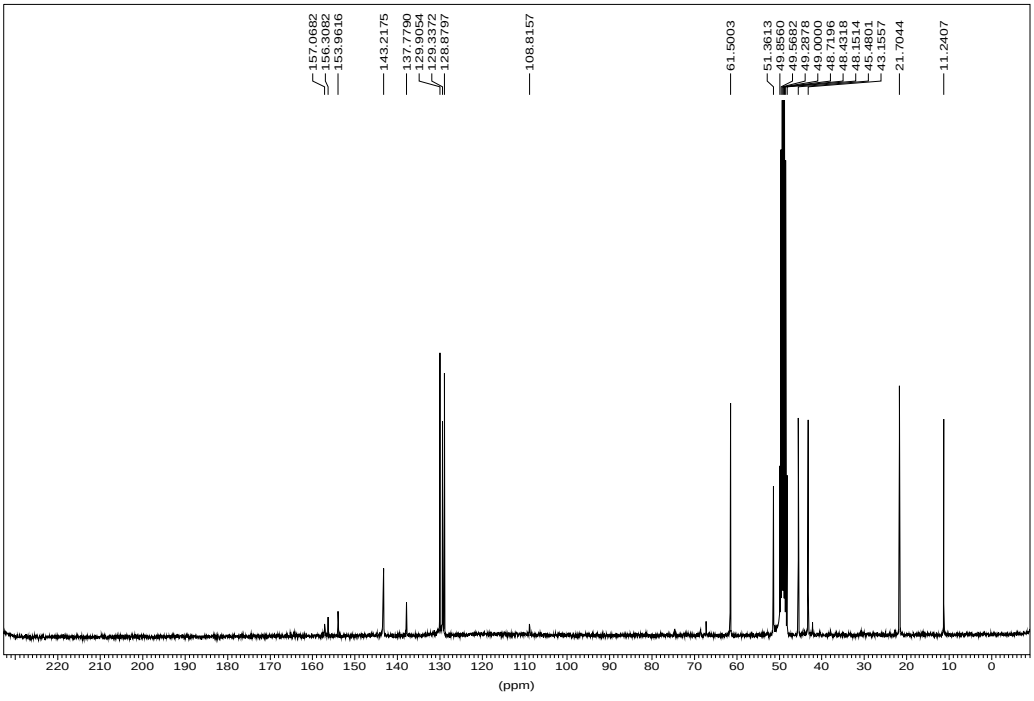
^{13}C NMR of **3-7b**



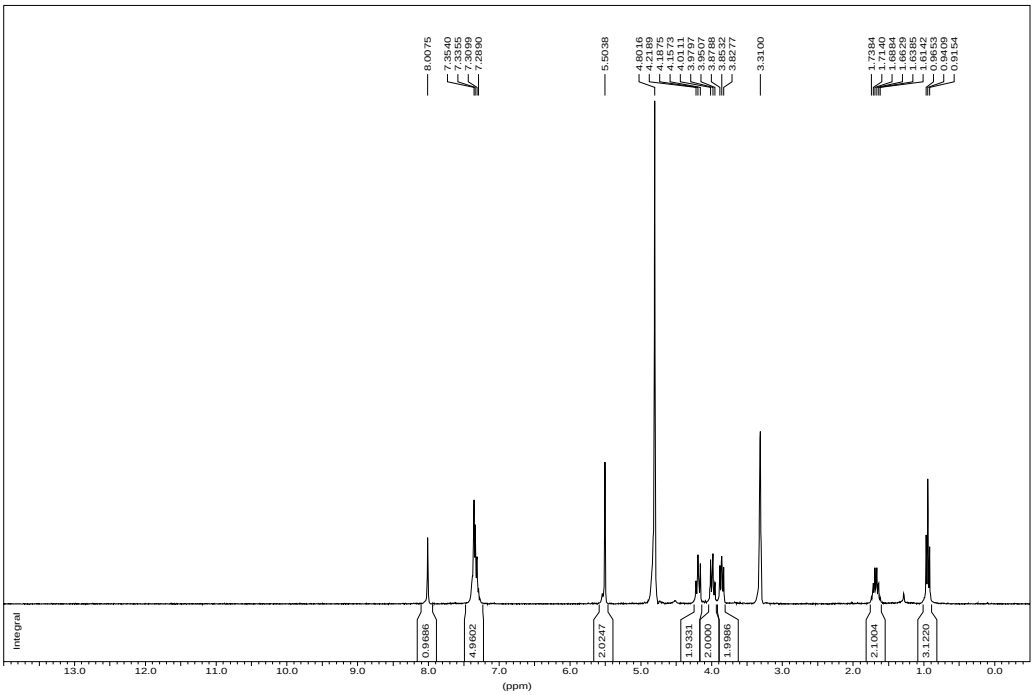
^{1}H NMR of **3-8a**



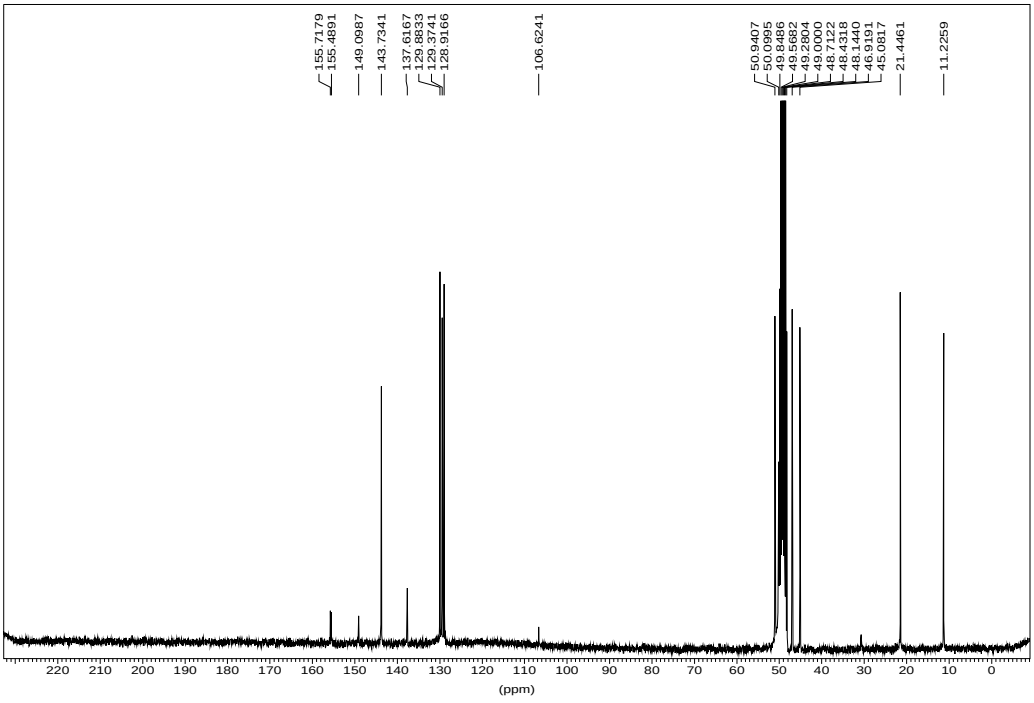
^{13}C NMR of **3-8a**



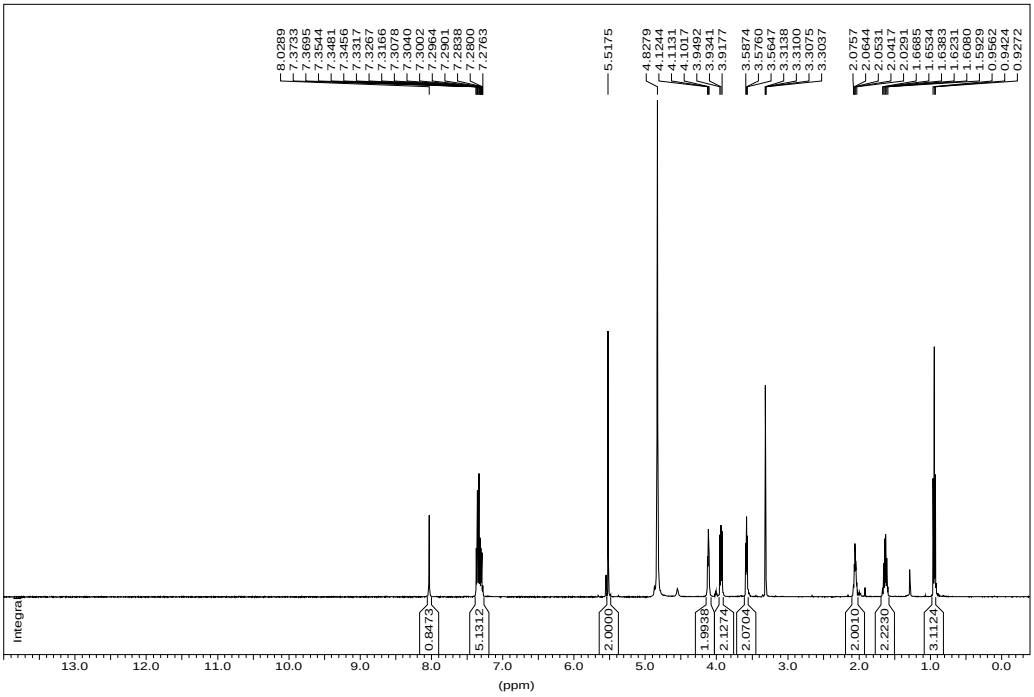
^{1}H NMR of **3-9a**



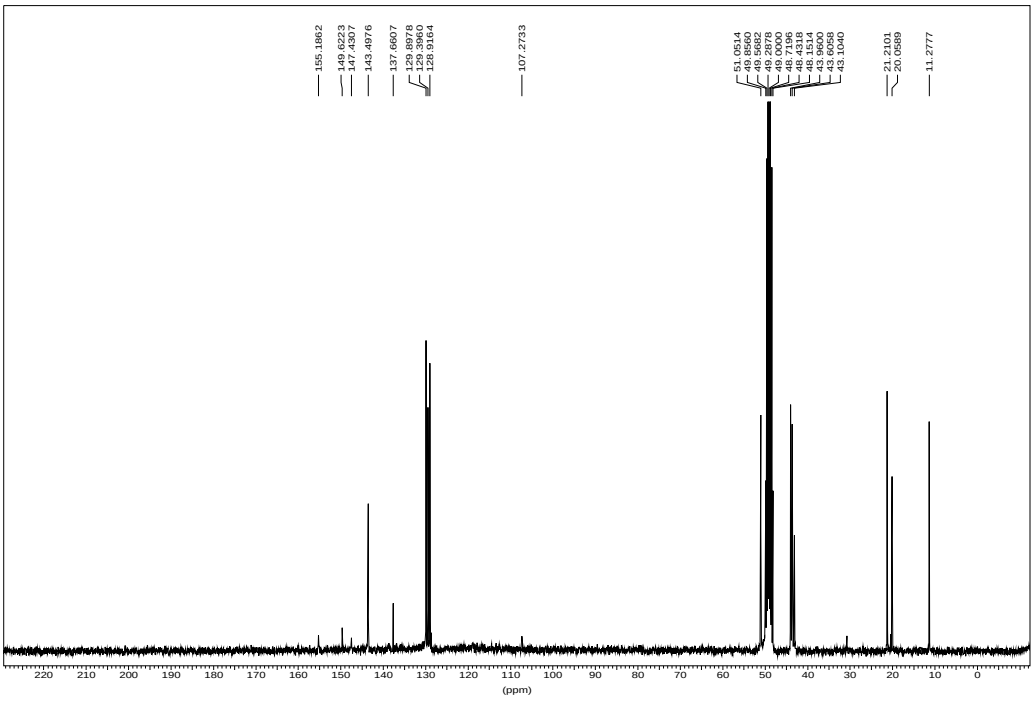
^{13}C NMR of **3-9a**



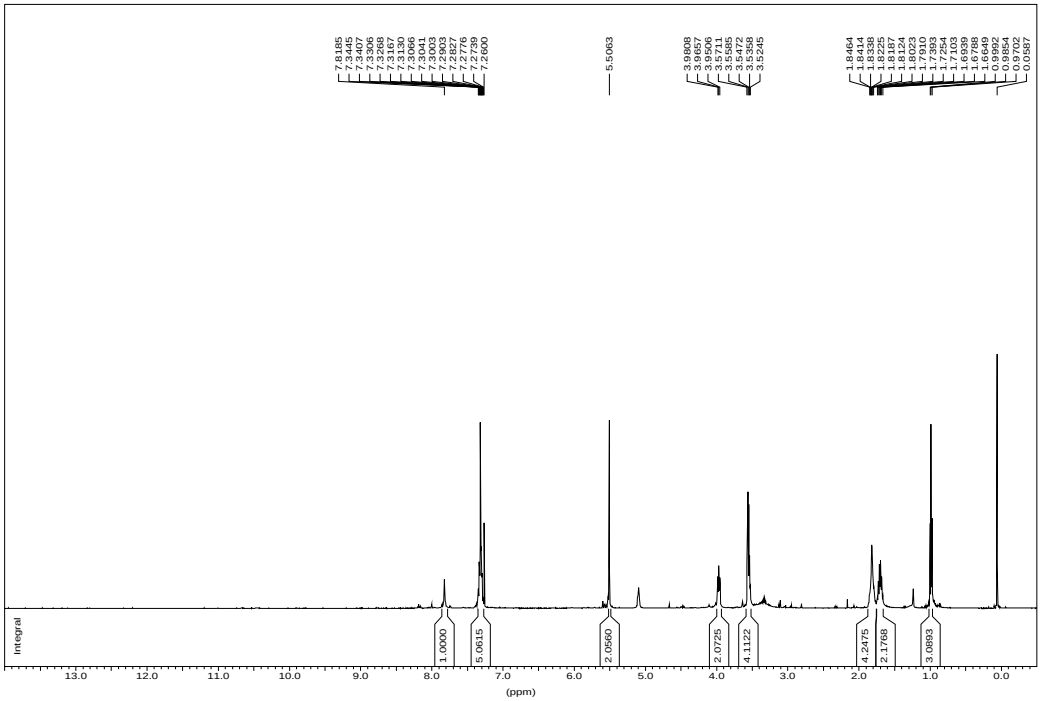
^{1}H NMR of **3-9b**



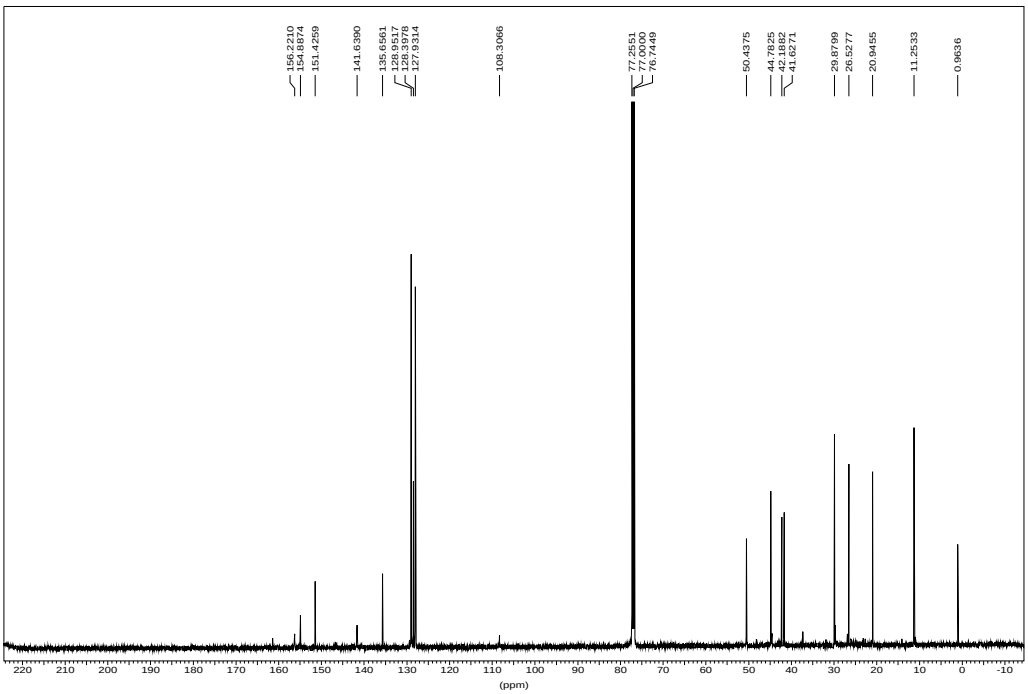
^{13}C NMR of **3-9b**



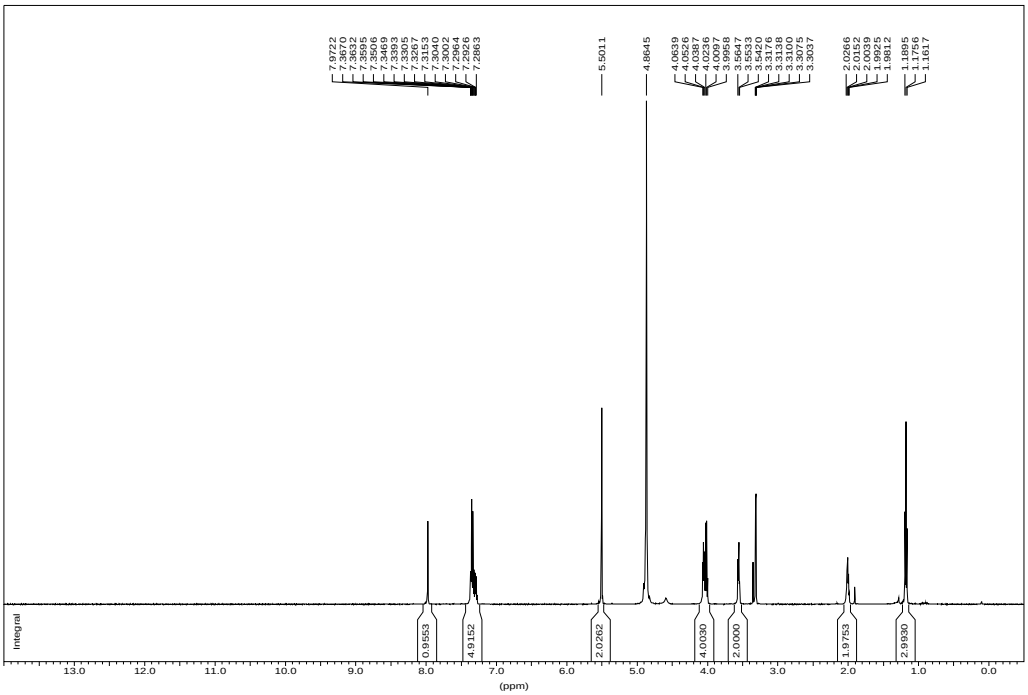
^{1}H NMR of **3-9c**



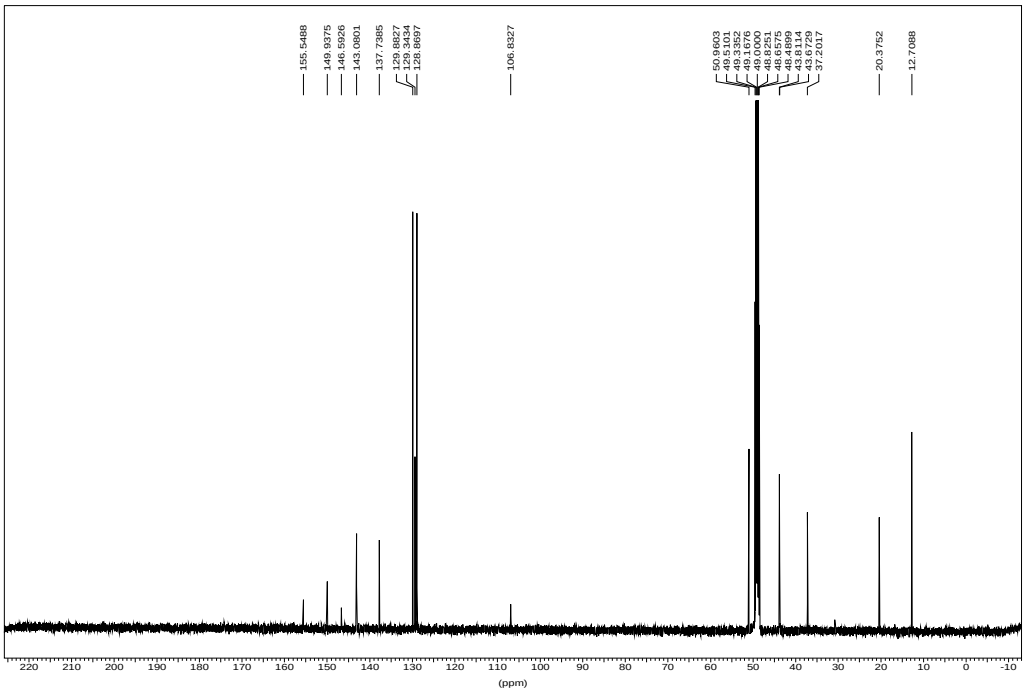
^{13}C NMR of **3-9c**



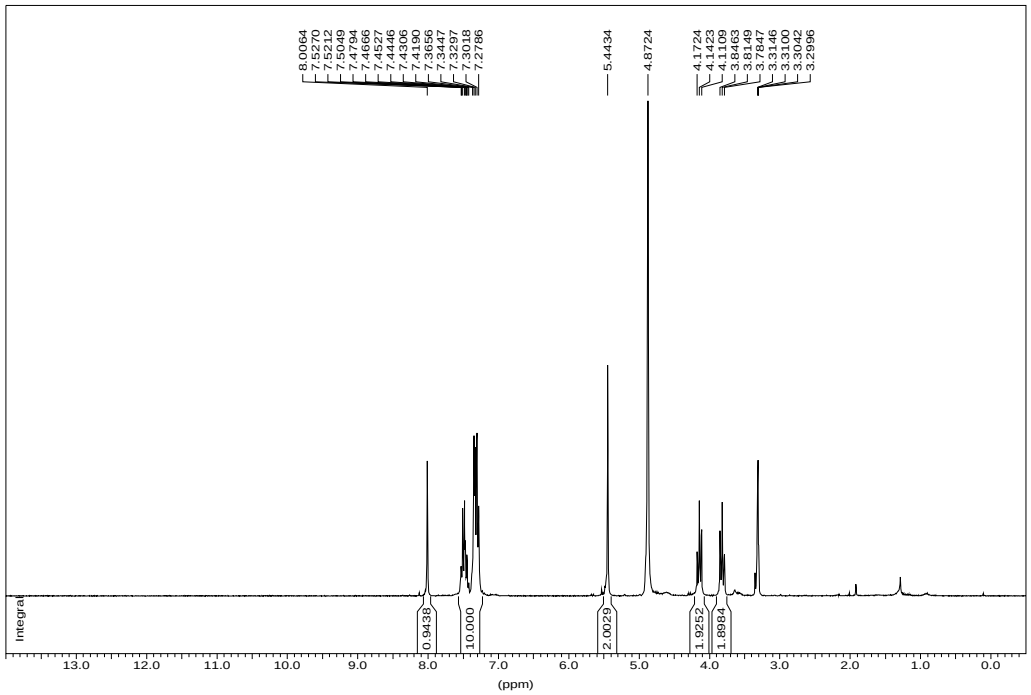
^{1}H NMR of **3-9d**



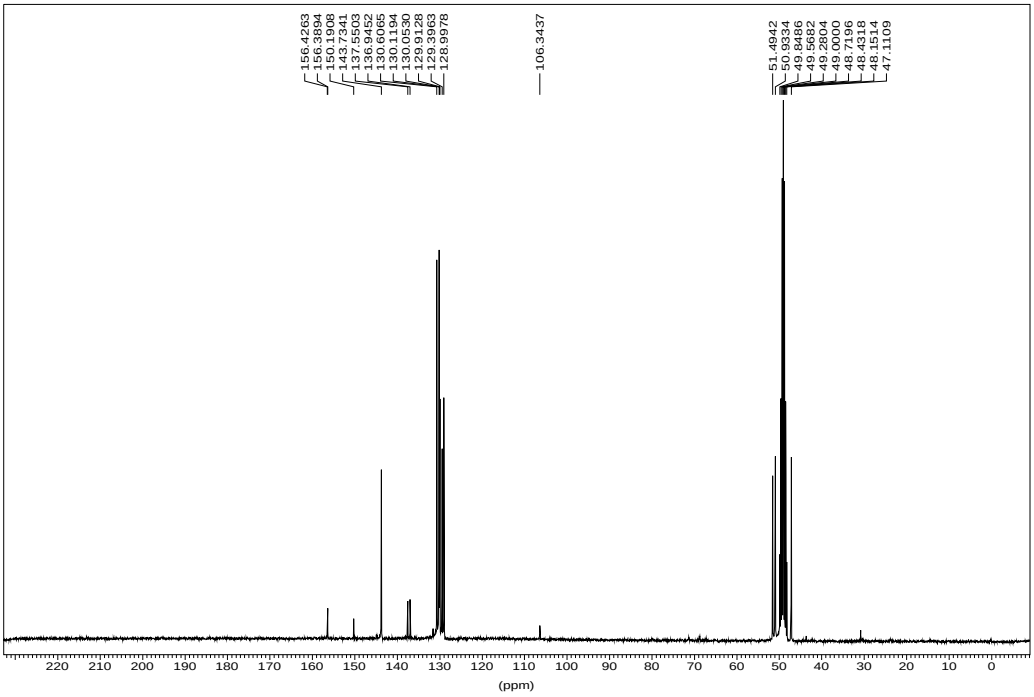
^{13}C NMR of **3-9d**



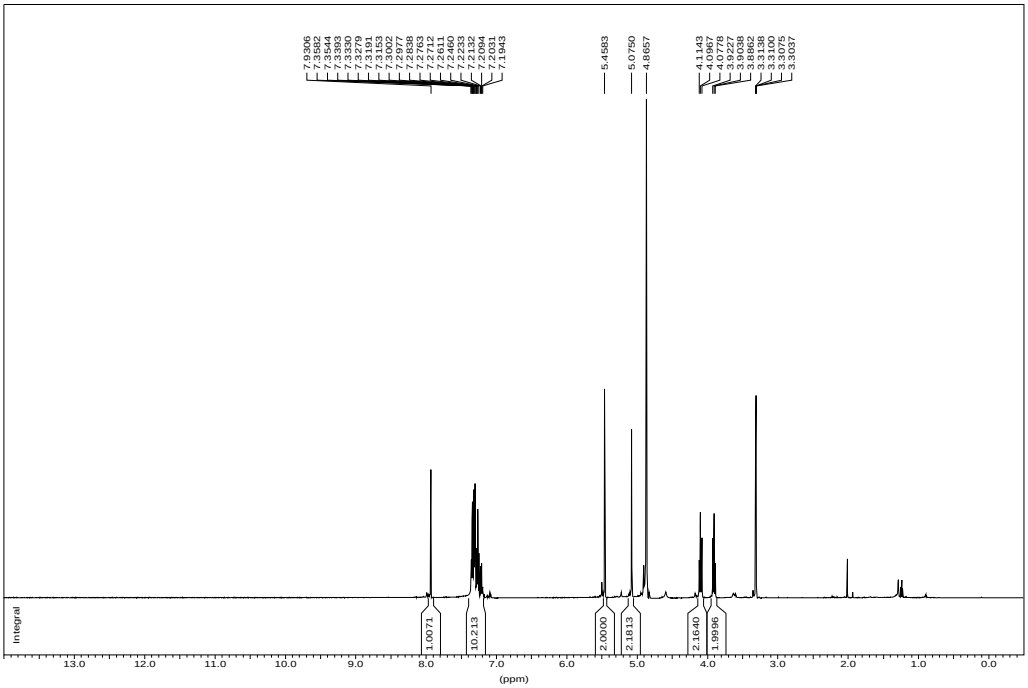
^{1}H NMR of **3-9e**



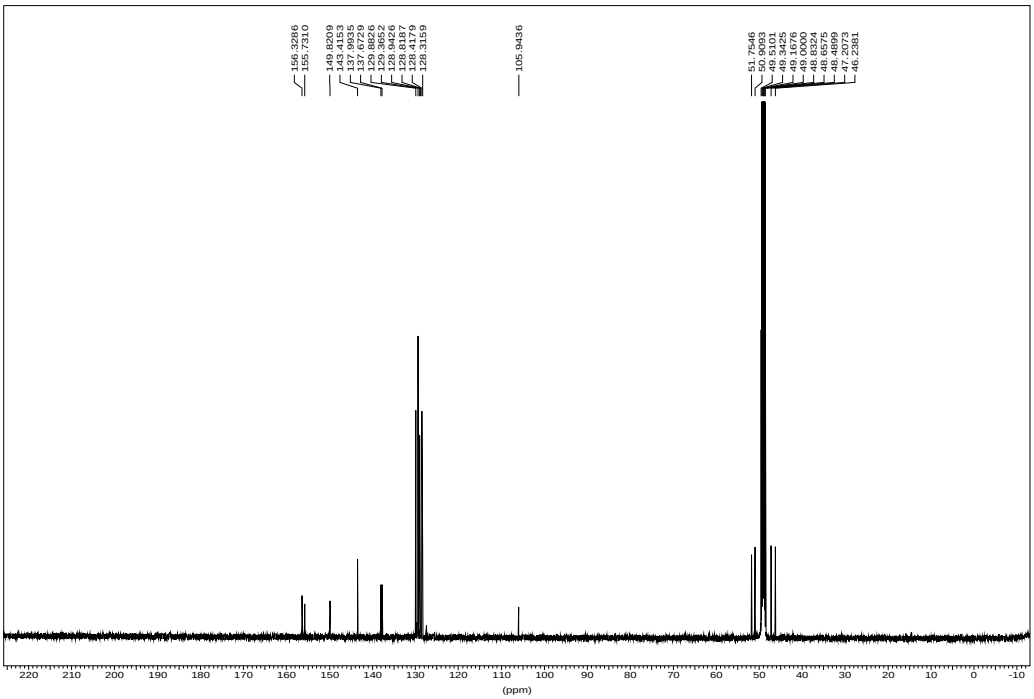
^{13}C NMR of **3-9e**



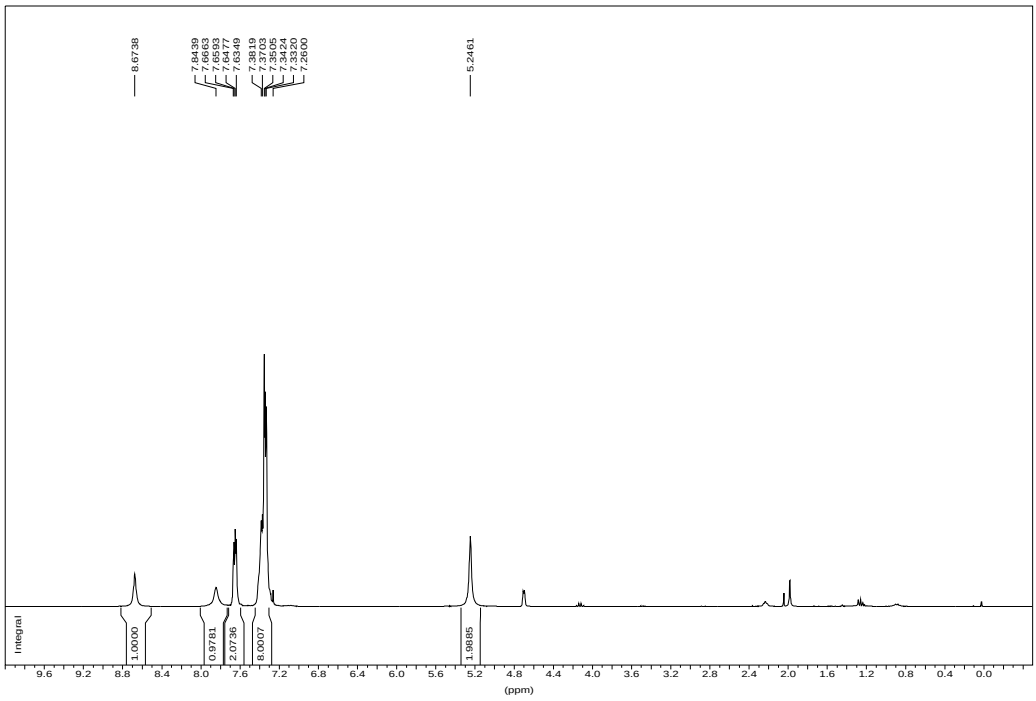
^{1}H NMR of **3-9f**



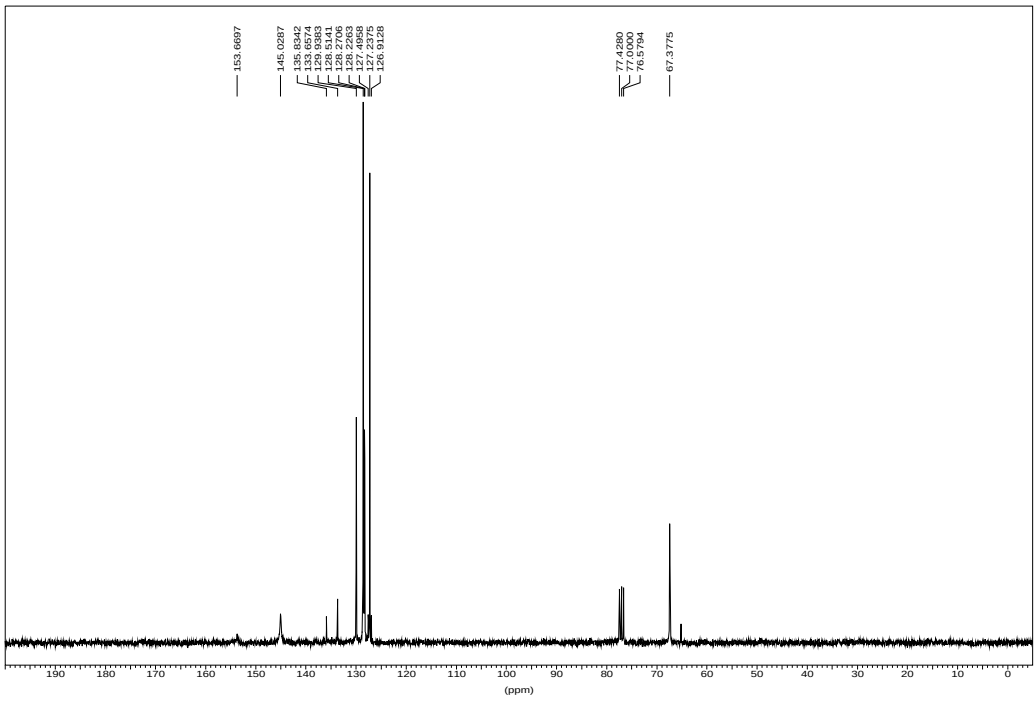
^{13}C NMR of **3-9f**



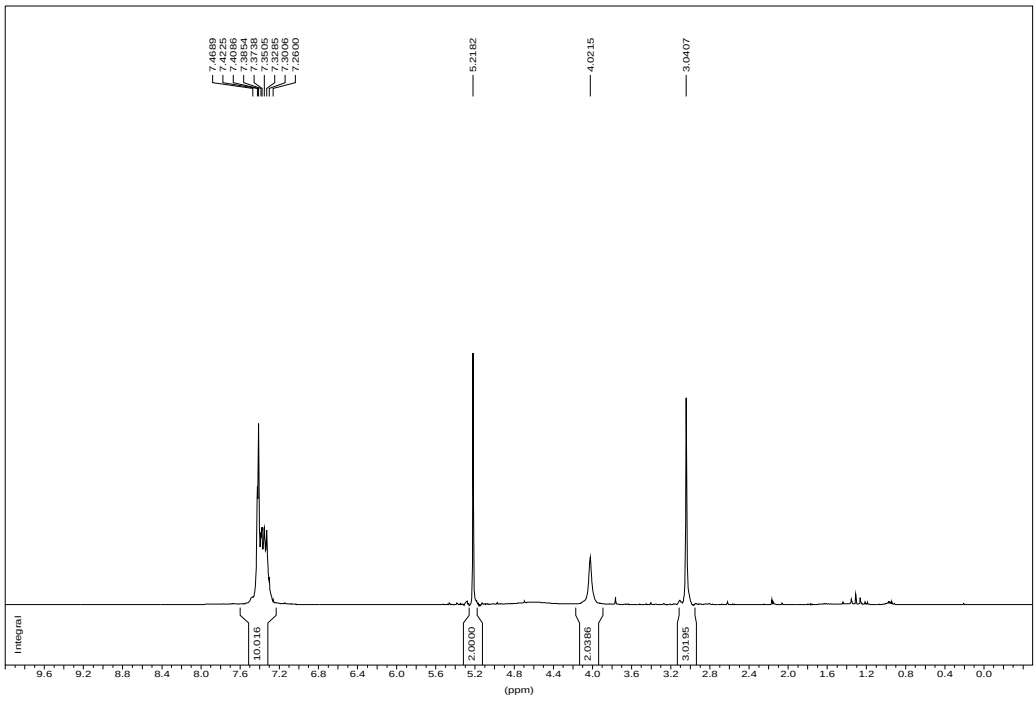
^{1}H NMR of **4-9**



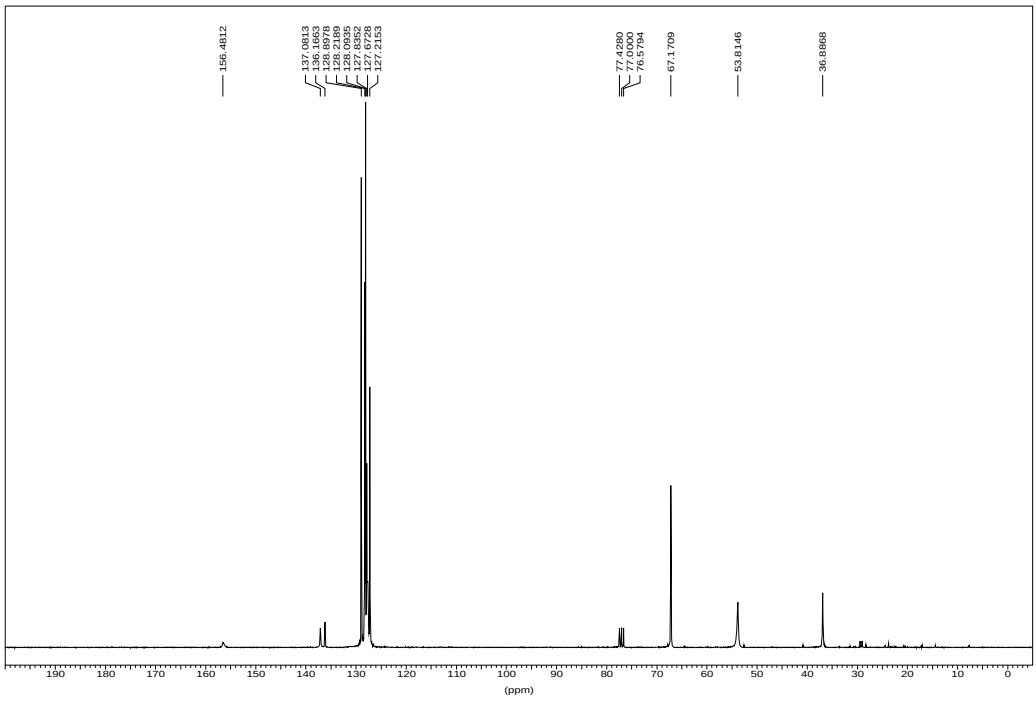
^{13}C NMR of **4-9**



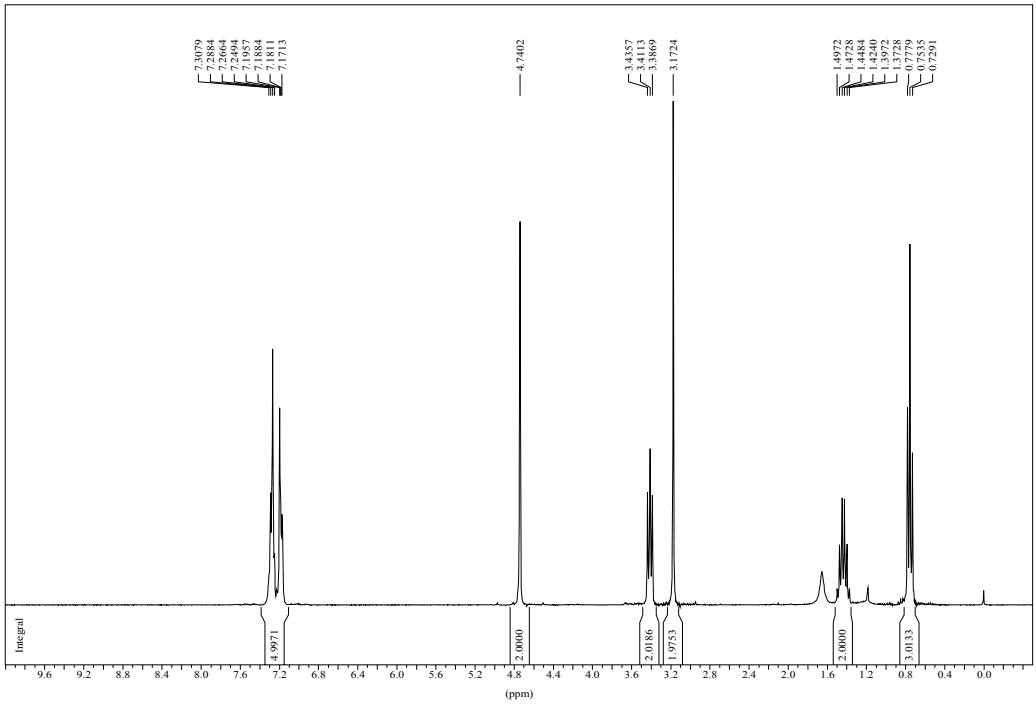
^{1}H NMR of **4-11**



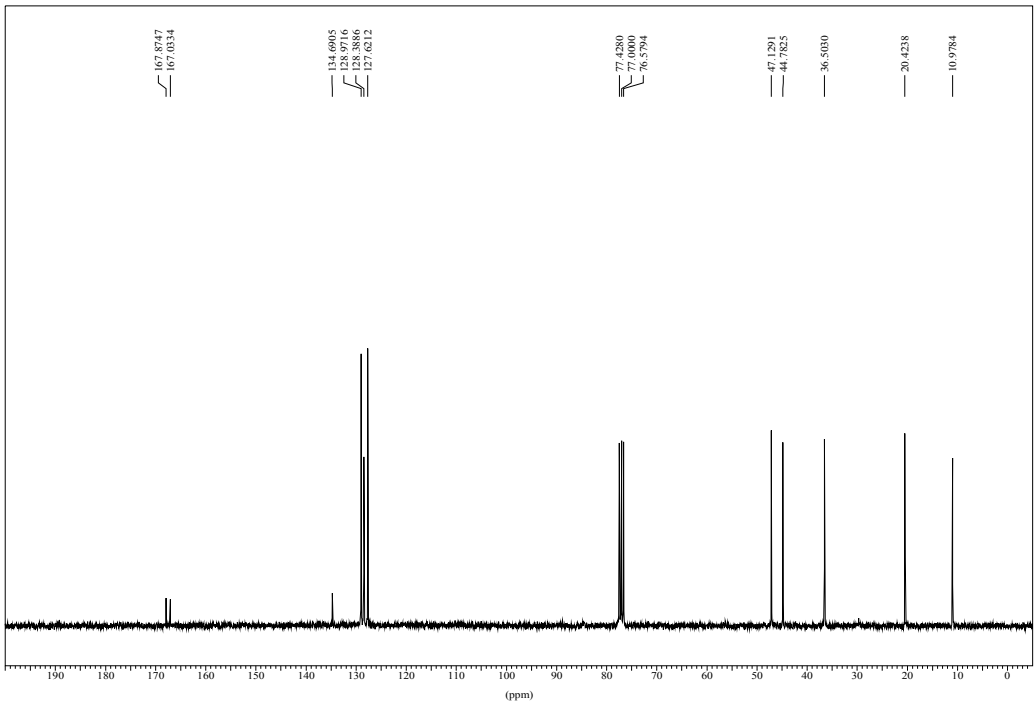
^{13}C NMR of **4-11**



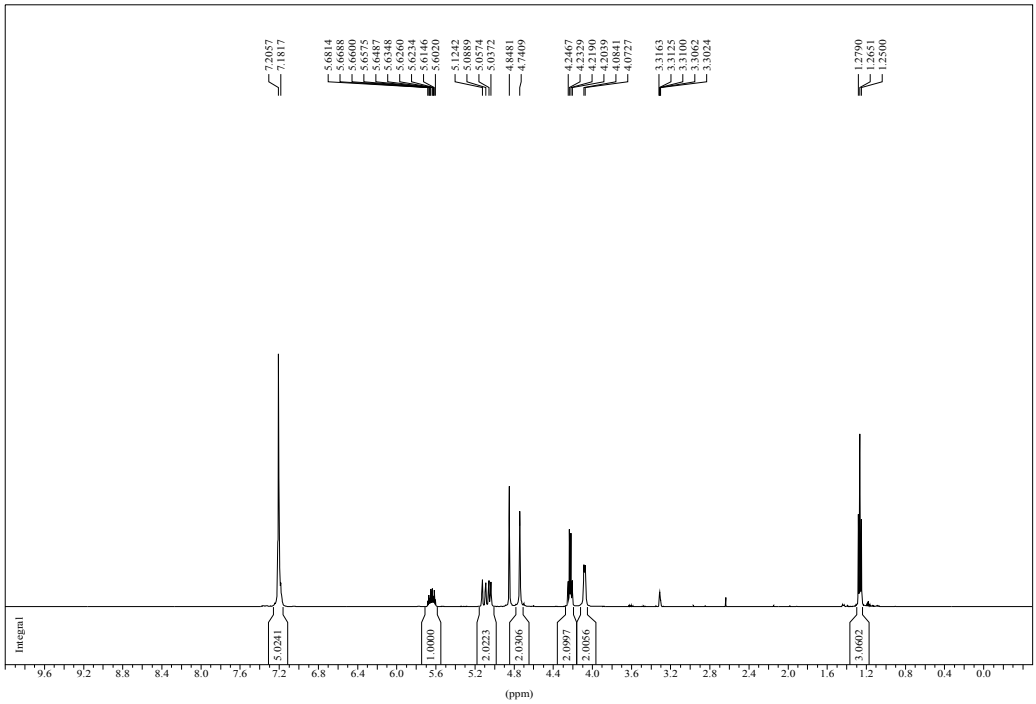
^{1}H NMR of **4-7-1c**



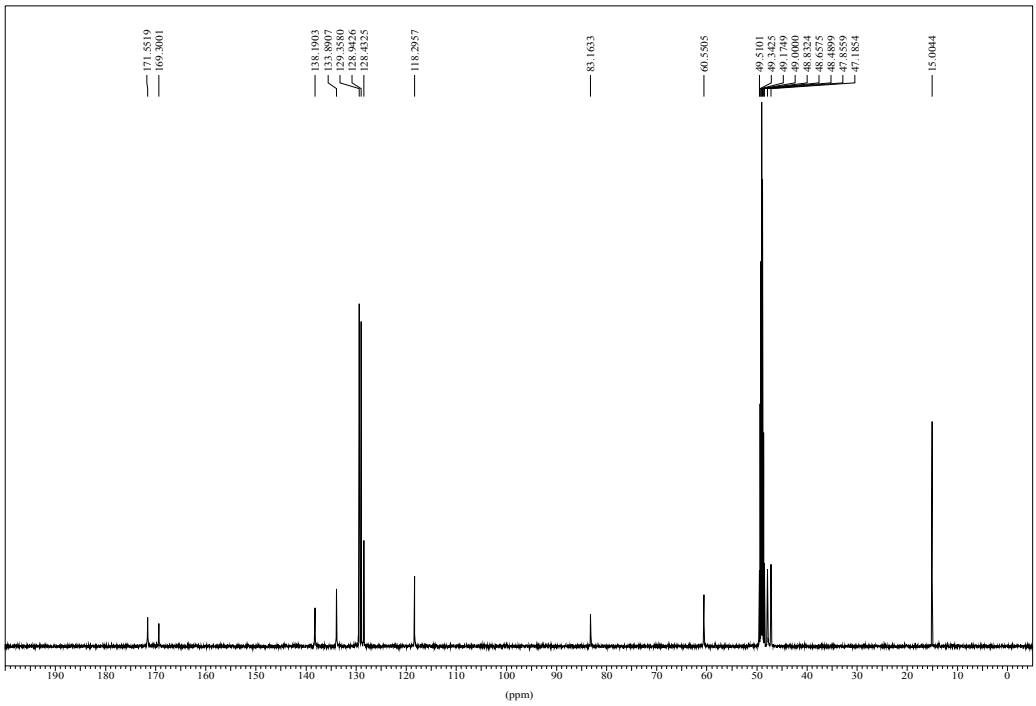
^{13}C NMR of **4-7-1c**



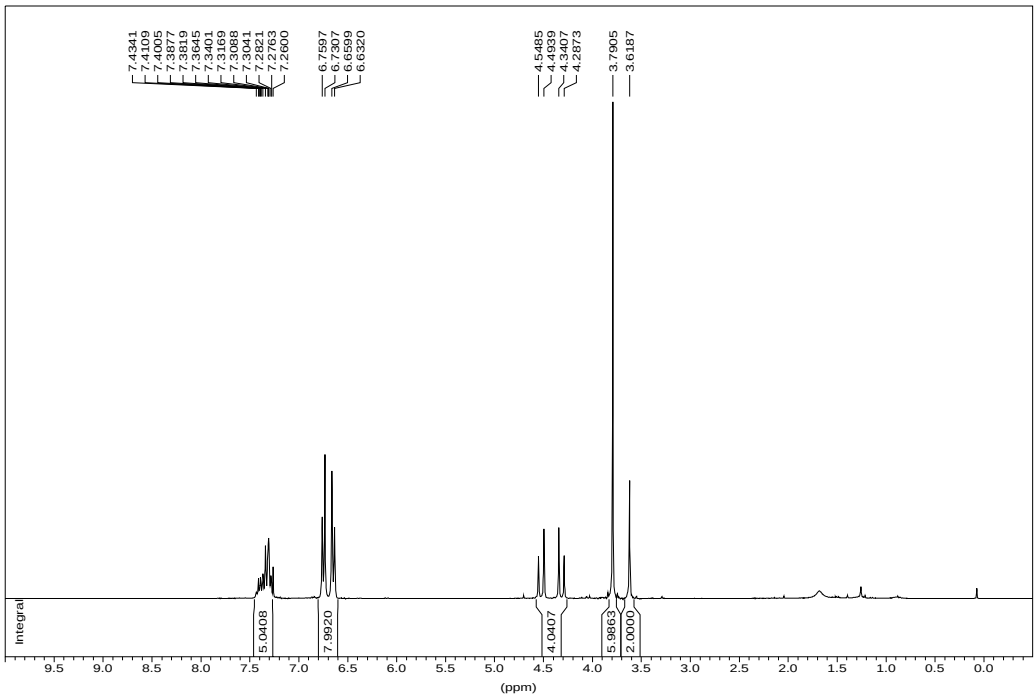
^{1}H NMR of **4-7-2b**



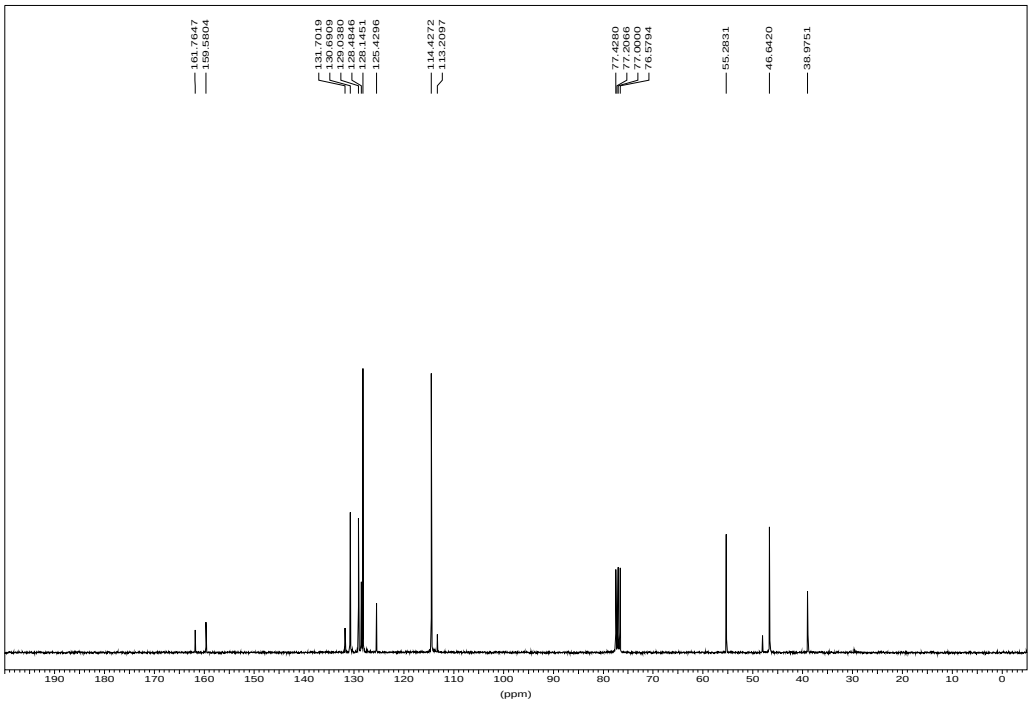
^{13}C NMR of **4-7-2b**



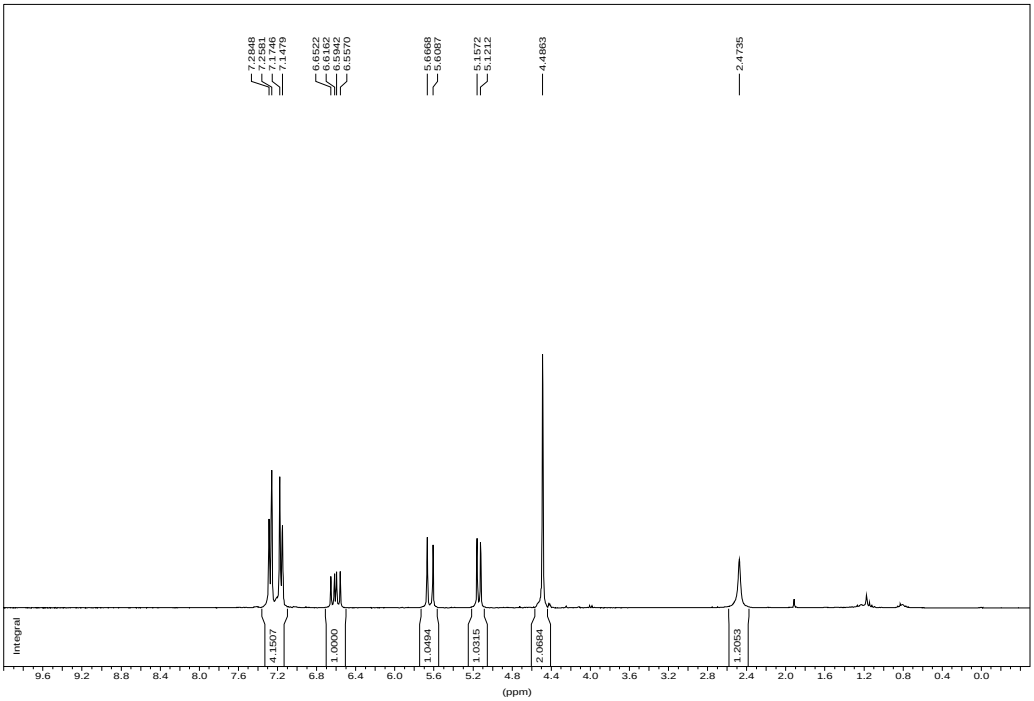
^{1}H NMR of **4-7-3e**



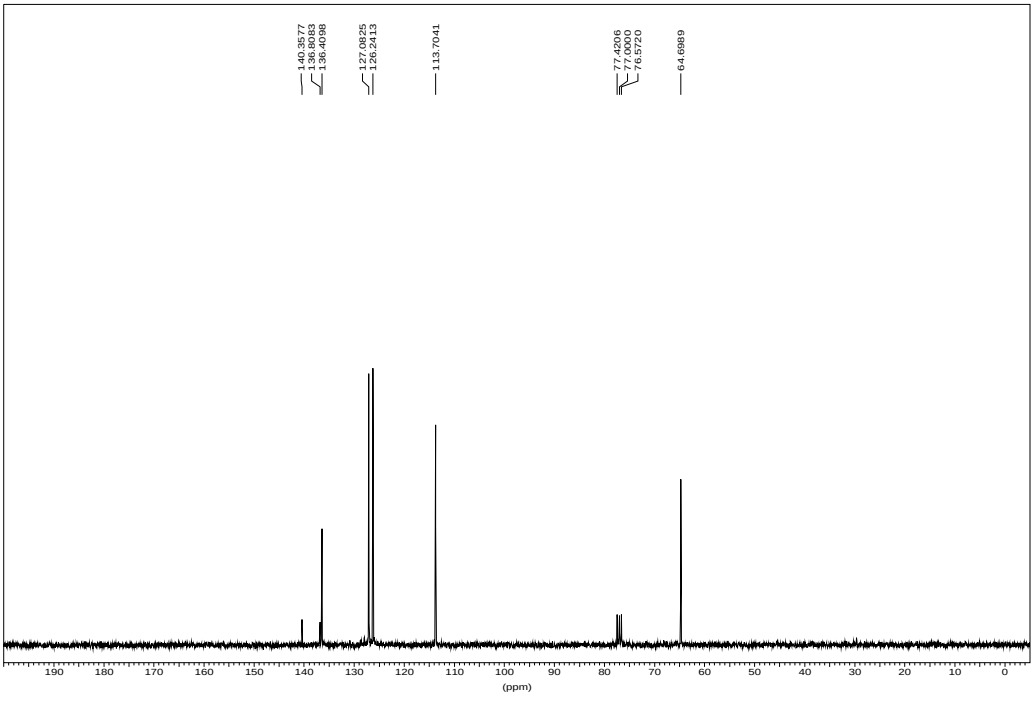
^{13}C NMR of **4-7-3e**



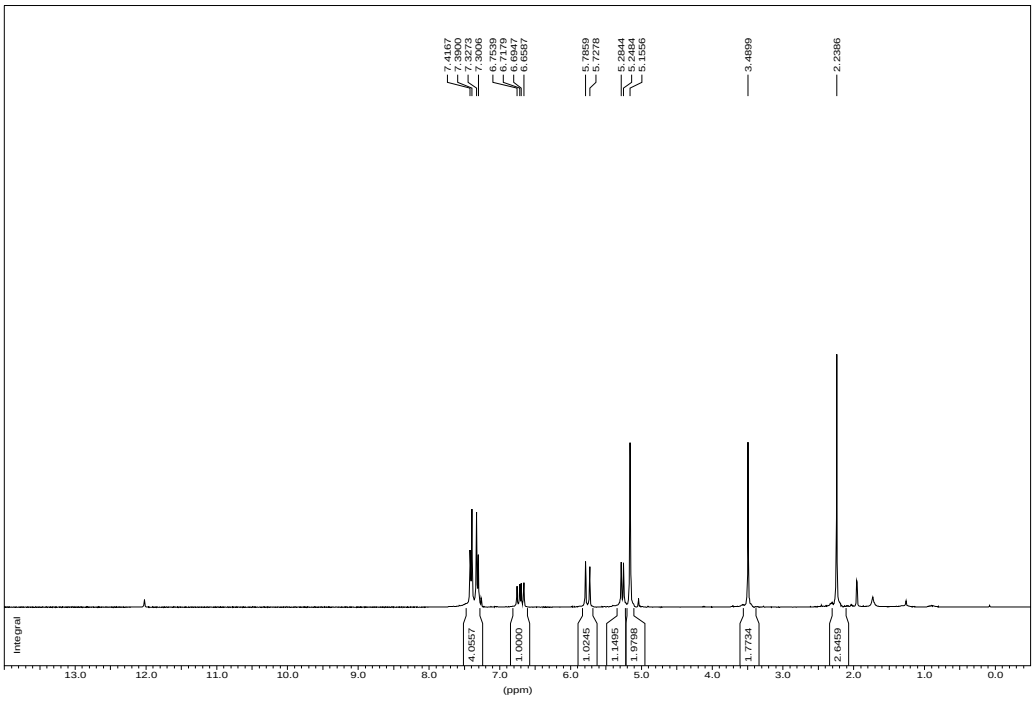
^{1}H NMR of **5-16**



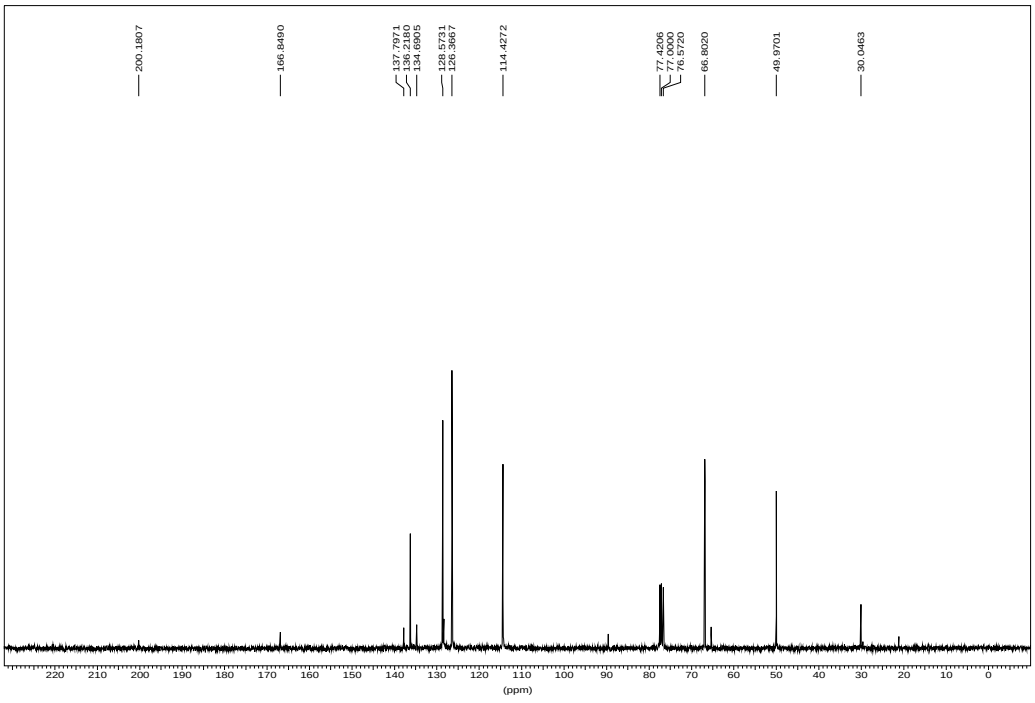
^{13}C NMR of **5-16**



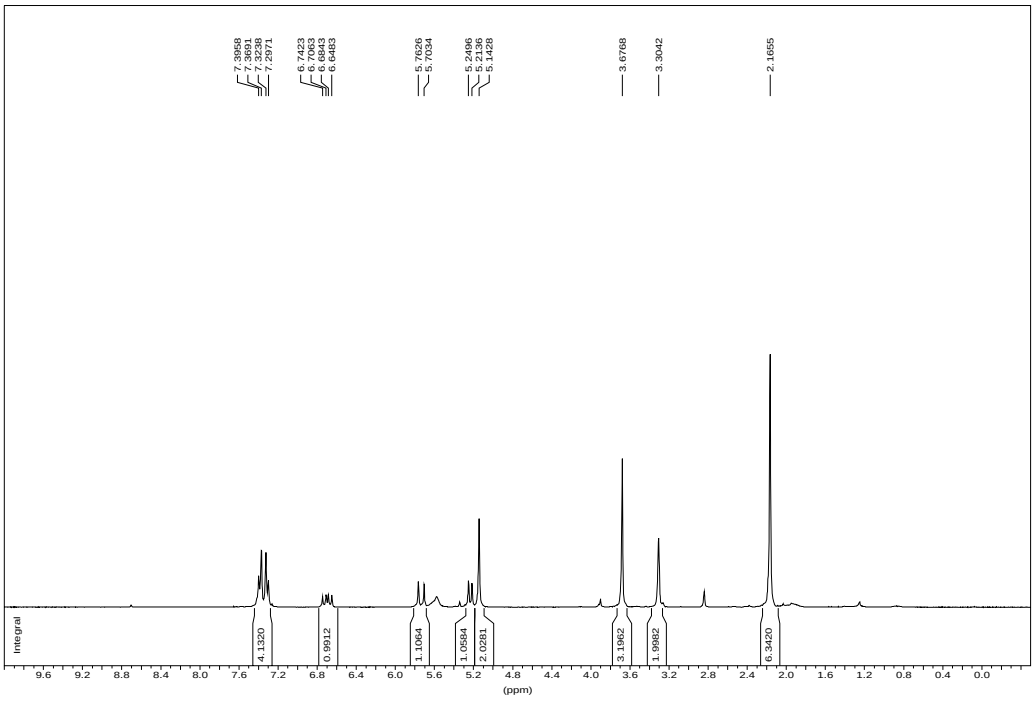
^{1}H NMR of **5-17**



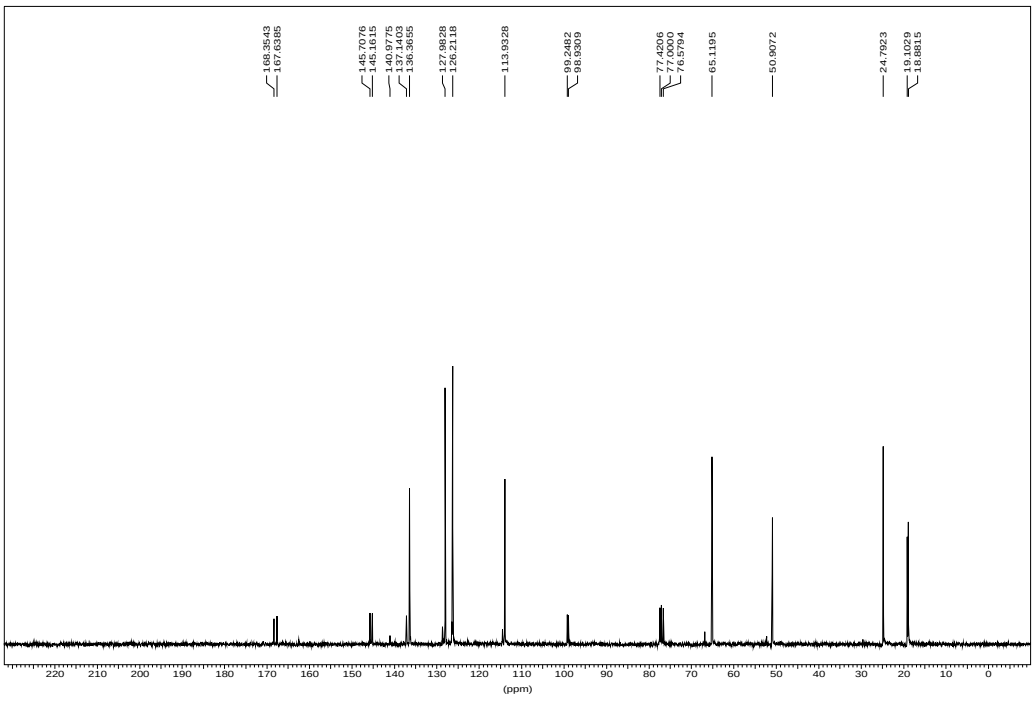
^{13}C NMR of **5-17**



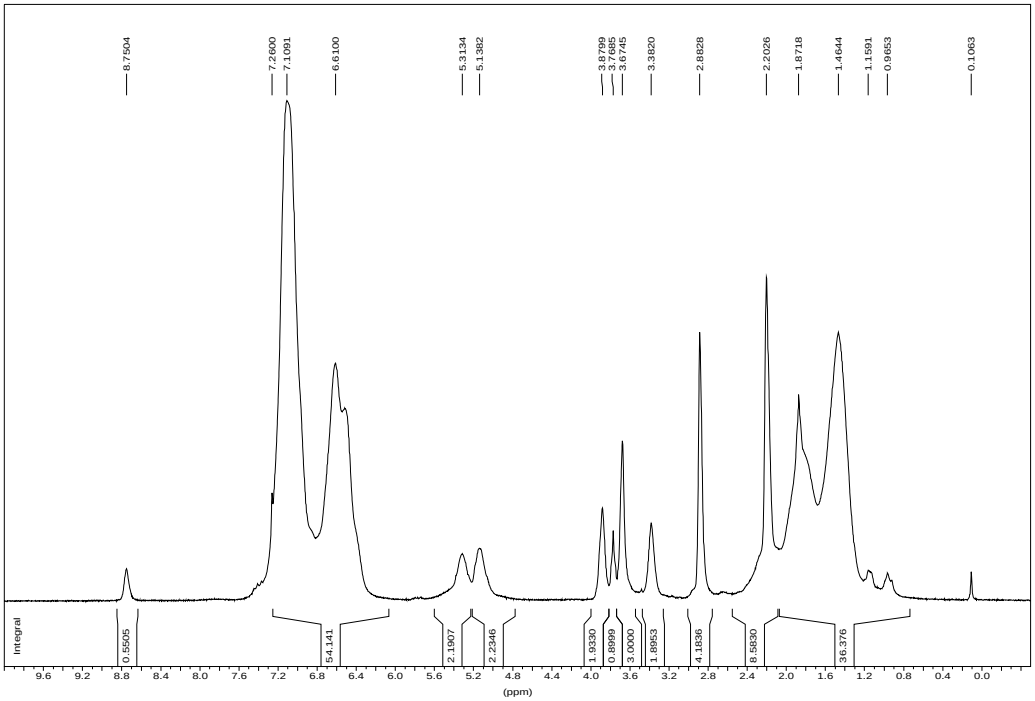
^{1}H NMR of **5-4**



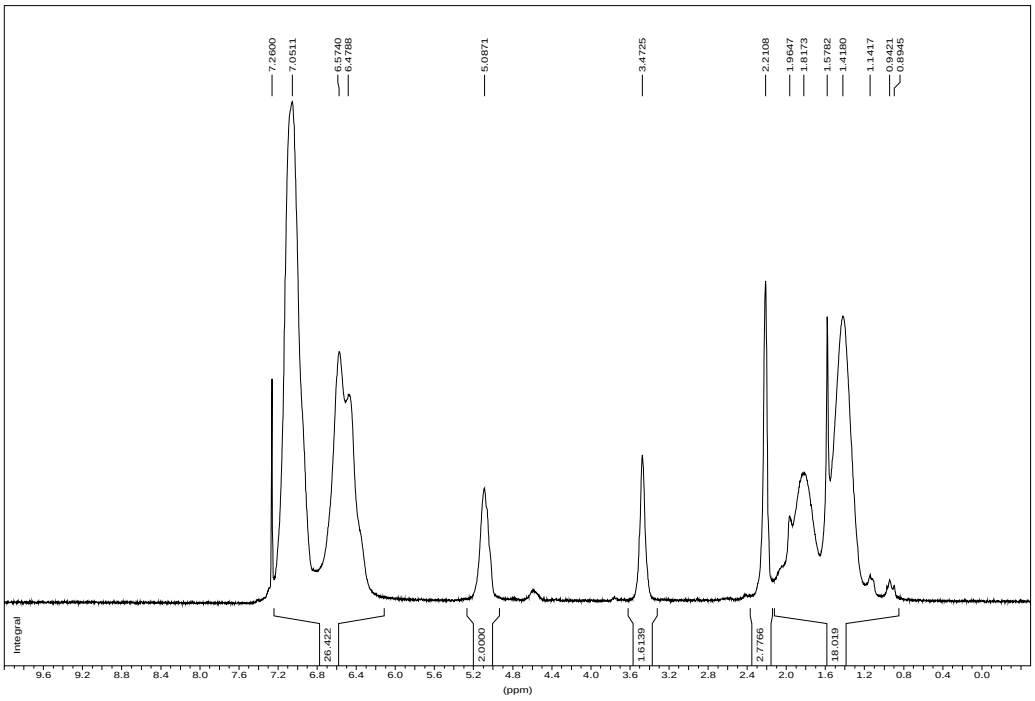
^{13}C NMR of **5-4**



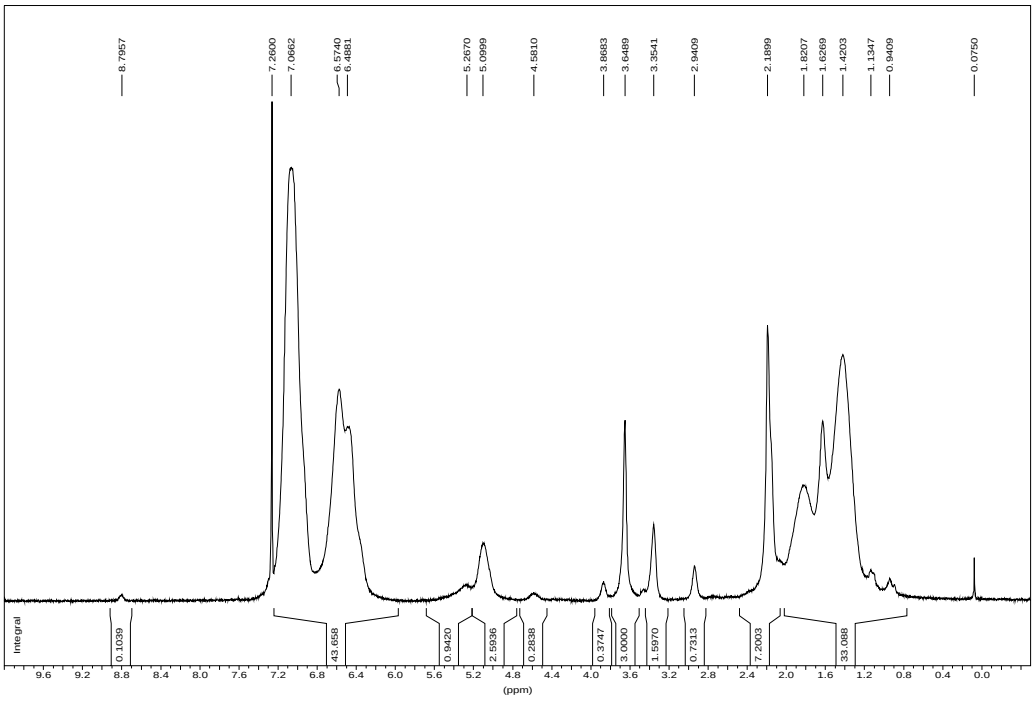
^{1}H NMR of **5-18**



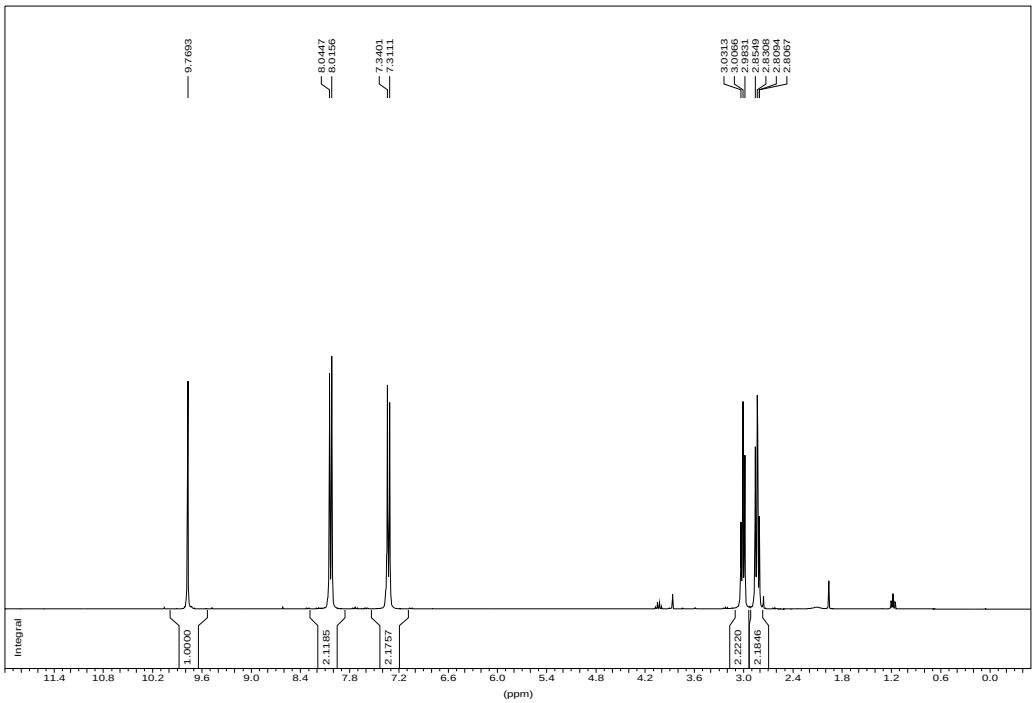
^{1}H NMR of **5-19**



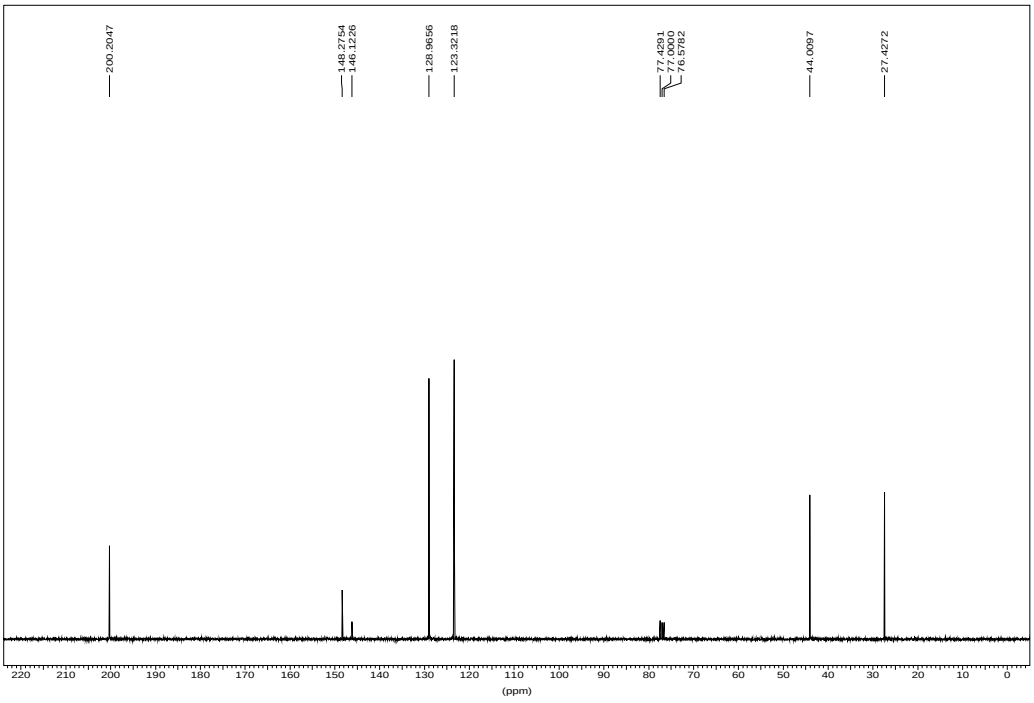
^{1}H NMR of **5-20**


8.7957
7.2600
7.0662
6.5740
6.4881
5.2670
5.0999
4.5810
3.8683
3.6489
3.3541
2.9409
2.1899
1.8207
1.6269
1.4203
1.1347
0.9409
0.0750
Integral
0.1039
43.658
0.9420
2.5936
0.2838
0.3747
3.0000
1.5970
0.7313
7.2003
33.088
(ppm)

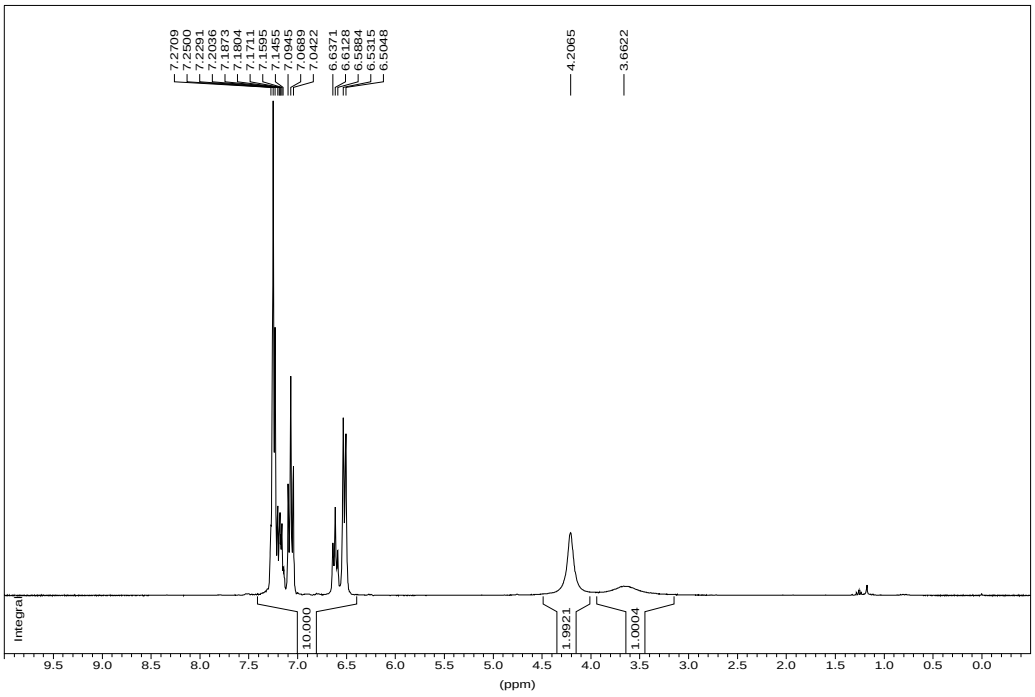
^{1}H NMR of **5-21a**



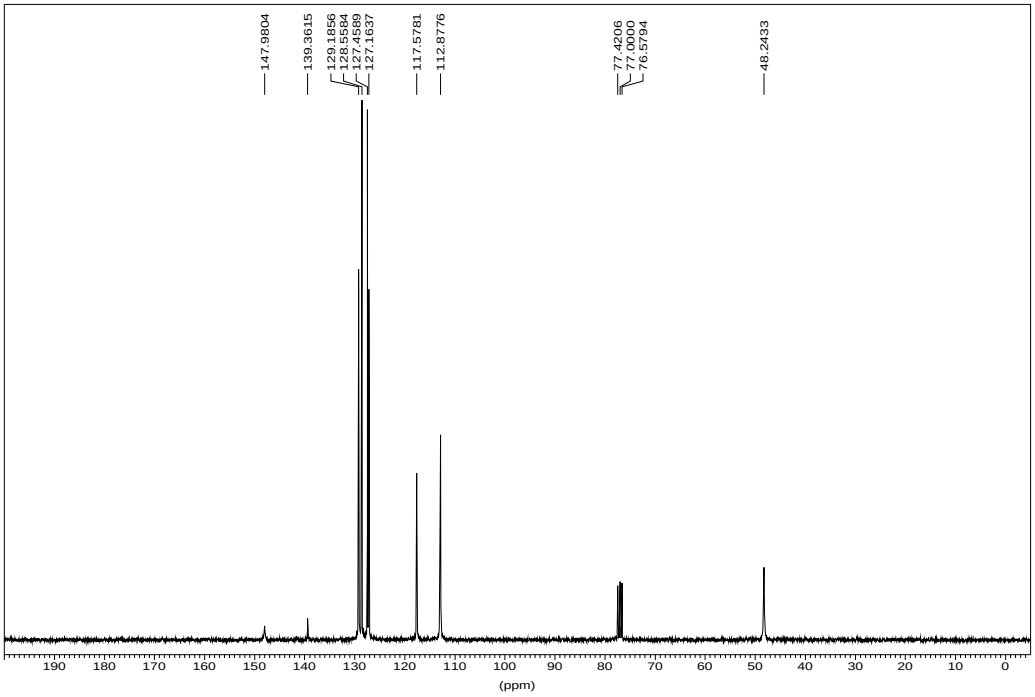
^{13}C NMR of **5-21a**



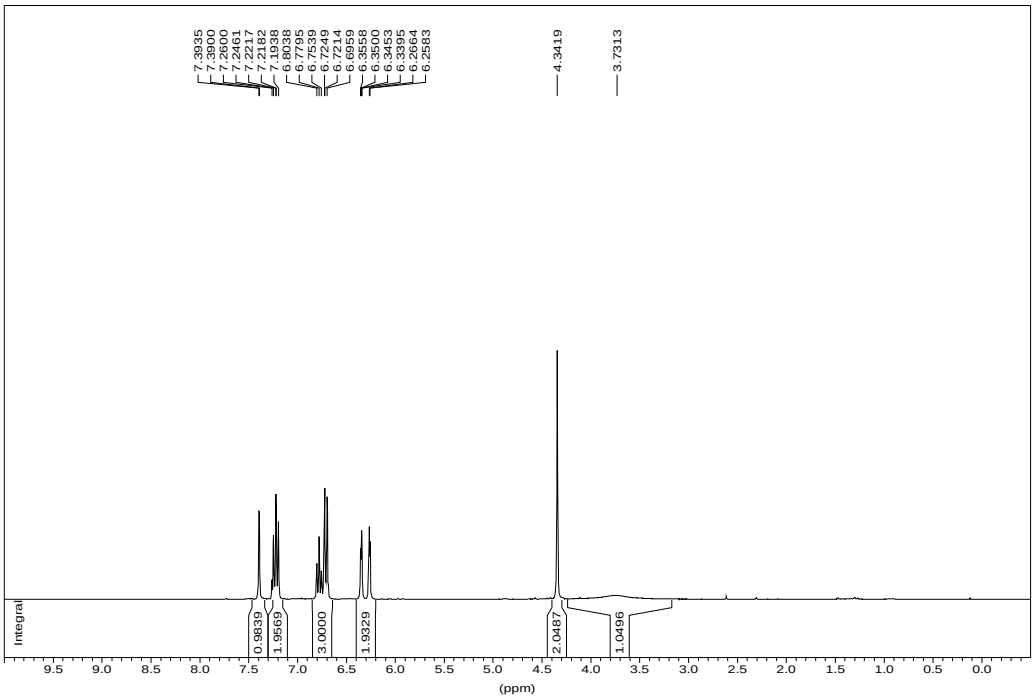
^{1}H NMR of **5-22a**



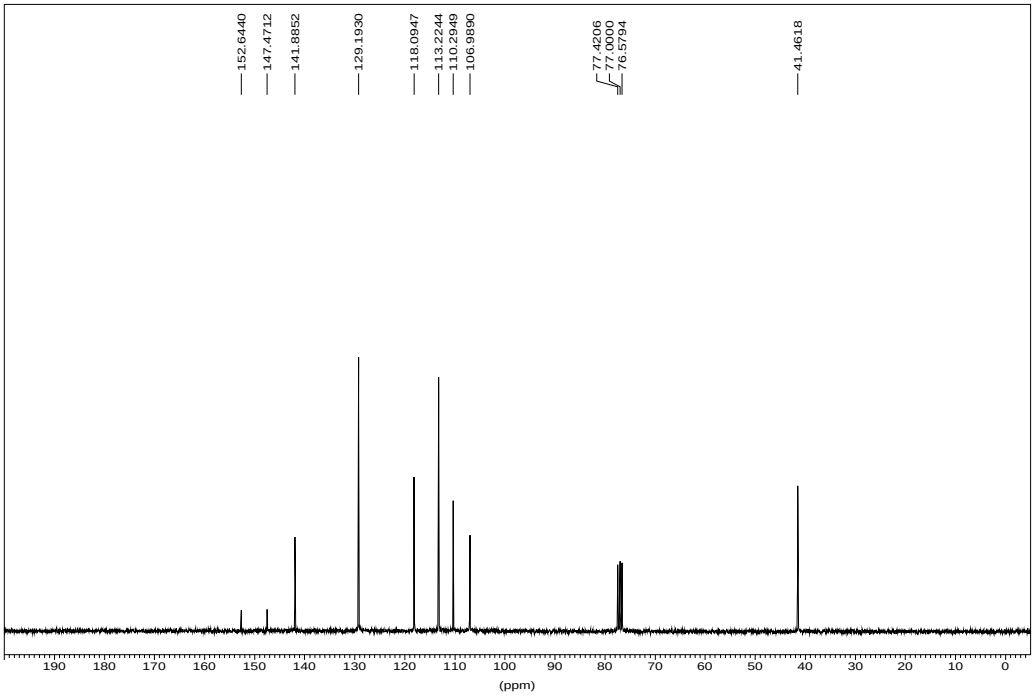
^{13}C NMR of **5-22a**



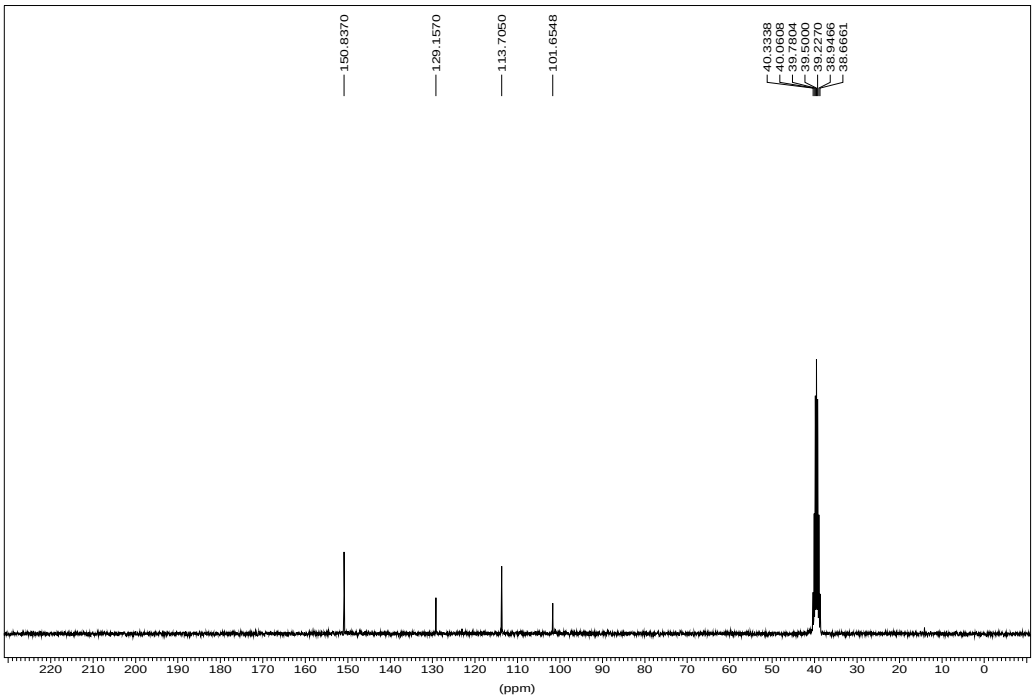
^{1}H NMR of **5-22e**



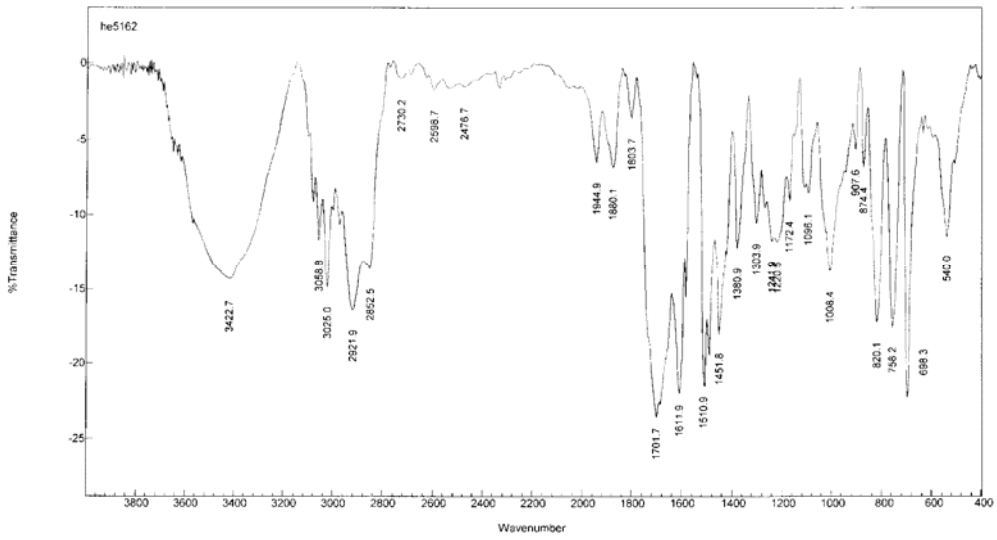
^{13}C NMR of **5-22e**



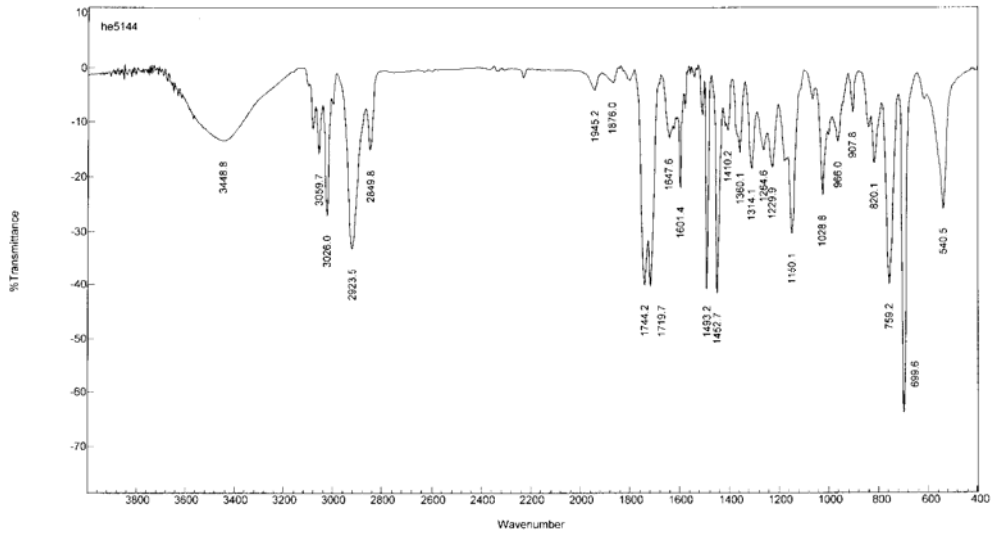
^{13}C NMR of **5-23**



IR Spectrum of 5-18



IR Spectrum of 5-19



IR Spectrum of 5-20